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CONTENTS ON INSIDE COVER

Including ALLERGY ABSTRACTS

The Journal of Allergy

CONTENTS FOR SEPTEMBER, 1947

AMERICAN ACADEMY OF ALLERGY

Third Annual Meeting, New York, N. Y., Nov. 25 to 27, 1946

(Continued)

Antigenic Fractions in Ragweed Pollen. III. Further Evidence of Immunologic Specificity of Fraction 1 and Fraction 2. William B. Sherman, M.D., and Arthur Stull, Ph.D., New York, N. Y. ---- 287

Chemical and Immunologic Studies of Low Ragweed Pollen Extract. H. S. Baldwin, A. W. Moyer, and P. F. deGara, New York, N. Y. With Technical Assistance of H. Brown and K. J. Winfield, Jr. 296

Skin Tests in Dogs With Common Allergens. Jose Cortez, M.D., Mexico City, Mexico, Matthew Brunner, M.D., Brooklyn, N. Y., and Irving Altman, D.V.M., Brooklyn, N. Y. ---------- 305

Pyribenzamine Versus Specific Hyposensitization in the Treatment of Pollinosis: A Comparative Study. Carl E. Arbesman, M.D., Victor L. Cohen, M.D., and Howard Osgood, M.D., Buffalo, N. Y. 311

Penicillin Aerosol in the Prevention and Treatment of Respiratory Infections in Allergic Patients. Samuel J. Prigal, M.D., Lawrence J. Morganbesser, M.D., and Frederic P. McIntyre, M.D., New York, N. Y. ---------- 325

Original Articles

Personality Factors in "Allergic" Disorders. John H. Mitchell, M.D., Charles A. Curran, Ph.D., William F. Mitchell, M.D., Iola Sivon, M.D., and Ruth Myers, B.S., Columbus, Ohio ---------- 337

Flour Allergy. Michael Schwartz, M.D., Copenhagen, Denmark ---- 341

Editorial

Editorial ---------- 351

American Academy of Allergy

News and Notes ---------- 352

Allergy Abstracts

Asthma and Hay Fever—Dermatology—Otorhinology and Ophthalmology—Miscellaneous Allergies—Anaphylaxis—Miscellaneous -- 49-60

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The Journal of Allergy

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American Academy of Allergy

Third Annual Meeting, New York, N. Y., Nov. 25 to 27, 1946

(Continued)

ANTIGENIC FRACTIONS IN RAGWEED POLLEN*

III. FURTHER EVIDENCE OF IMMUNOLOGIC SPECIFICITY OF FRACTION 1 AND FRACTION 2

WILLIAM B. SHERMAN, M.D., AND ARTHUR STULL, PH.D., NEW YORK, N. Y.

PREVIOUS papers[1, 2] have described in detail the separation and chemical properties of three fractions separated from ragweed pollen. Fraction 1 and Fraction 2 were readily water soluble. Highly purified preparations contained approximately 12 per cent nitrogen, were free from reducing sugars, and gave many protein tests. These fractions were separated by many reprecipitations with ammonium sulfate, Fraction 1 from 0 to 50 per cent saturation and Fraction 2 from 50 to 100 per cent saturation. Fraction 1 was quantitatively precipitated by trichloracetic acid and by phosphotungstic acid, while Fraction 2 was not precipitated by trichloracetic acid, but precipitated quantitatively with phosphotungstic acid. The precipitation of Fraction 1 but not Fraction 2 by trichloracetic acid and the inactivation of Fraction 1 but not Fraction 2 by heating at 70° C. at pH4 were the criteria of the purity of the preparations of the fractions used in the present study.

The alkali soluble Fraction 3, which precipitated at pH4, gave positive skin reactions in a few ragweed hay fever cases. It failed[2] specifically to sensitize guinea pigs as determined by the Dale test, and the lack of ragweed sensitive serums which react sufficiently with this fraction has prevented a complete study of its immunologic specificity. The work here reported was confined to Fraction 1 and Fraction 2, which appear to be the important antigens in cases of ragweed hay fever.

The antigenic specificity of these fractions has been shown[1, 2] by direct skin tests and passive transfer studies with the serums of ragweed sensitive patients, and by blocking antibody titrations[3] in serums taken from patients treated with whole ragweed extract. This paper describes the studies of specific

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blocking antibodies, in patients treated with the separate fractions, as well as in a larger number of ragweed cases treated with whole extract, and immunologic studies of the serums of rabbits injected with the separate fractions, the results confirming the specificity and completeness of the separation of ragweed antigens, previously[1, 2] shown in guinea pigs by means of the Dale technique.

REACTIONS OF SERUMS OF RAGWEED-SENSITIVE PATIENTS WITH RAGWEED POLLEN FRACTIONS IN PASSIVE TRANSFER

For passive transfer studies, duplicate sites were made with the serums of 200 ragweed-sensitive patients in the skin of normal test subjects and tested with solutions of Fraction 1 and Fraction 2, containing 10 millimicrograms of protein nitrogen per ml. (1 protein nitrogen unit per ml.[4]), following the technique described in previous papers.[1-3] This dilution of the testing extracts was chosen because Fraction 1 in this dilution reacted with almost all highly sensitive ragweed serums, while the degree of reaction to Fraction 2 varied widely. A negative reaction with this dilution of Fraction 2 did not necessarily mean a complete absence of sensitivity, for if a more concentrated extract was used, a higher percentage of positive reactions was obtained. Although a number of test subjects were used, the reactions of each serum to the two fractions were always tested on the same test subject.

One hundred eighty-eight of the 200 serums gave positive reactions with this dilution of Fraction 1, nine gave questionable (±) reactions, and three no reaction. With this dilution of Fraction 2, eighty-two serums gave positive reactions, 23 questionable (±) reactions, and 95 gave no reaction. One hundred fifty-five of the serums gave larger reactions to Fraction 1 than to Fraction 2, eight gave larger reactions to Fraction 2, and 37 gave essentially equal reactions to the two fractions. Except for the fact that the reactions were generally more active to Fraction 1 than to Fraction 2, there was no correlation between the reactions of different serums to the two fractions, and the fact that some serums gave more reaction to Fraction 2 than to Fraction 1 indicated that the two fractions acted as independent antigens. The results, which are summarized in Table I, were consistent with the belief that the two fractions act as independent antigens, Fraction 1 being the more active antigen.*

The extremes of variation of reactivity of different serums with the two fractions were determined by testing sites made with the serum with serial dilutions of each fraction until no further reaction was obtained. With one serum, Fraction 1 was 1,000 times as reactive as Fraction 2, while with another serum Fraction 2 was 100 times as reactive as Fraction 1, as shown in Table II. This was further evidence that the two fractions are independently antigenic.

Direct intracutaneous tests on ragweed-sensitive patients with the pollen fractions, in appropriate dilutions, showed wide variations in the relative reactions to Fraction 1 and Fraction 2, Fraction 2 giving reactions in many cases

*One hundred and forty-four of these serums were also tested with Fraction 3 in the same dilution; of these, one gave a three plus reaction, 7 two plus reactions, 10 one plus reactions, 6 questionable (±) reactions, and 120 no reaction. This indicated that Fraction 3 was a relatively unimportant factor in ragweed pollen allergy, and the paucity of serums reacting actively with this fraction has hampered studies of the antibody response of patients to this fraction.

as active as those to Fraction 1, and occasionally it was more active. In other cases it gave little or no reaction. In general, these results paralleled those obtained on passive transfer, confirming the impression that the two fractions acted as independent antigens, but the differences in reaction on direct skin tests were less clear cut than on passive transfer and gave no additional information.

TABLE I. REACTIONS OF RAGWEED-SENSITIVE SERUMS TO FRACTIONS 1 AND 2 IN PASSIVE TRANSFER

REACTION TO FRACTION 1	REACTION TO FRACTION 2				
	+++	++	+	±	0
++++ (5 cases)	2	1	1	0	1
+++ (45 cases)	5	9	7	4	20
++ (86 cases)	3	15	23	13	32
+ (52 cases)	2	3	11	3	33
± (9 cases)	0	0	0	3	6
0 (3 cases)	0	0	0	0	3
Total 200 Cases	12	28	42	23	95

TABLE II. EXTREMES OF VARIATION OF REACTIONS OF SERUMS TO FRACTIONS 1 AND 2

SERUM	TESTED WITH	100 UNITS*	10 UNITS	1 UNIT	0.1 UNIT	0.01 UNIT
A	Fraction 1	-	-	++	+	0
A	Fraction 2	+	0	0	-	-
B	Fraction 1	+	0	0	-	-
B	Fraction 2	++	++	+	0	-

*Protein nitrogen units per ml.

DEVELOPMENT OF BLOCKING ANTIBODY IN RAGWEED SENSITIVE PATIENTS AFTER INJECTIONS OF THE RAGWEED POLLEN FRACTIONS AND WHOLE RAGWEED EXTRACT

Definite evidence of the immunologic specificity of the two ragweed pollen fractions was demonstrated by studies of the development of blocking antibody[5] (thermostable antibody[6]), in ragweed sensitive patients after series of injections of the separate fractions of low ragweed pollen and of ordinary ragweed pollen extract (equal parts of low ragweed and giant ragweed). Previous studies at this clinic and elsewhere have shown the immune antibody of allergic humans to be specific,[5] and the presence of distinct antibodies for the two ragweed pollen fractions has been demonstrated in the serums of patients treated with whole ragweed extract.[3] In studies of the clinical use of the ragweed pollen fractions, 18 previously untreated patients with typical ragweed hay fever were given preseasonal treatment for one season with weekly injections of solution of low ragweed Fraction 1. The dosage, on a protein nitrogen basis, was adjusted to the degree of clinical sensitivity, as indicated by skin tests,[7] and increased according to the individual patient's tolerance, as in the use of ordinary pollen extract, no allowance being made for the fact that only about 25 per cent[2]

of the protein of whole ragweed extract is Fraction 1. Another group of 17 previously untreated patients was similarly treated with Fraction 2 of low ragweed pollen. The clinical relief of hay fever produced by injections of the separate fractions, and the constitutional reactions resulting from such treatment will be discussed in other publications. The evaluation of clinical relief of hay fever is too difficult and subject to too great error to be considered evidence of the specificity of the ragweed pollen fractions, but in general the results were consistent with the belief that the two fractions were independent antigens and that relief was obtained only when the patient was treated with the fraction or fractions to which he was sensitive.

After three to four months of treatment when a dosage of 500 to 10,000 protein nitrogen units had been reached, serum was taken from the patients and tested for the presence of blocking antibodies, using the two pollen fractions separately as antigens. These tests were carried out by a method previously described,[3] heating the serum to destroy the skin sensitizing antibody, mixing it with suitable dilutions of each pollen fraction, and testing the reactions of these mixtures in skin sites passively sensitized with an unheated serum reacting strongly with both fractions. The reactions of the mixtures made with the serum of treated patients were compared with similar mixtures made with serum from the same patient before treatment and with normal control serums from non-allergic, untreated individuals.

The serums taken from ragweed-sensitive patients before treatment gave results identical with the normal control serums, indicating that no blocking antibody was present before treatment. The results of the tests on the serums taken after treatment with the separate fractions and on serums from a number of patients treated with the whole ragweed extract are summarized in Table III. No attempt was made to estimate the amount of blocking antibody, the results being recorded simply as positive, negative or doubtful. Of 18 patients treated with Fraction 1, seventeen developed antibody to this fraction. Serums of 15 of these patients were also tested with Fraction 2, none of these showed definite evidence of an immune antibody to Fraction 2. Of the 17 patients treated with Fraction 2, six developed definite evidence of blocking antibody to that fraction and two more gave doubtful reactions. Fourteen of these serums were also tested against Fraction 1, none blocked that fraction.

TABLE III. BLOCKING ANTIBODY IN SERUMS OF RAGWEED-SENSITIVE PATIENTS AFTER INJECTIONS OF FRACTIONS 1 AND 2 AND WHOLE RAGWEED POLLEN EXTRACT

TREATED WITH	CASES	ANTIBODY TO FRACTION 1			ANTIBODY TO FRACTION 2		
		PRESENT	DOUBTFUL	ABSENT	PRESENT	DOUBTFUL	ABSENT
Fraction 1 4 months	18	17	0	1	0	2	13
Fraction 2 4 months	17	0	1	13	6	2	9
Whole Ragweed 4 months	45	34	3	8	2	2	41
Whole Ragweed Several Seasons	24	20	0	0	7	3	5

Note: Not all patients in each group were tested for both antibodies.

It was apparent that injection of either fraction of the ragweed pollen produced a specific blocking antibody for that fraction and not for the other fraction, but that Fraction 1 was a more active antigen and produced antibody in practically all cases, while Fraction 2 produced a demonstrable antibody in less than one-half of the patients during the first three months treatment.

When both fractions were injected together, in treatment with the whole extract, most of the patients developed demonstrable blocking antibody to Fraction 1 within three to four months, while relatively few showed antibody to Fraction 2 at this time. As shown in Table III, 34 of 45 patients treated with whole extract showed blocking antibody to Fraction 1 the first season, while only two developed antibody to Fraction 2. However, when the same treatment was repeated for several successive years, or was continued with monthly injection of pollen extract throughout the year for several years, a higher percentage of patients developed a demonstrable antibody to Fraction 2. This was evident in the group of 15 such patients included in Table III.

In a previous publication[8] serums from nonsensitive individuals injected over a period of three months with large amounts of low ragweed pollen extract were reported to show the presence of blocking antibody to whole extract but no skin-sensitizing antibody. Two such serums were tested for blocking antibody against Fraction 1 and Fraction 2, and antibody to Fraction 1 but not to Fraction 2 was found.

In an occasional case, it was found that the serum of a treated patient gave reactions indicating the presence of blocking antibody to Fraction 1 or Fraction 2 when the serum-antigen mixtures were tested on skin sites sensitized with one serum, but that the same mixtures gave negative results when tested on sites sensitized with another serum. This variation was analogous to variations found previously when whole low ragweed pollen extract was used as antigen in studies of blocking antibody.[3] In that instance, it was found that the variations depended on whether the serum used to sensitize the sites was reactive with both fractions of the ragweed pollen or only one, and that observation was one of the early evidences of the antigenic specificity of the two fractions in humans. In the present study, it was believed that these variations indicated the presence of more than one antigenic group in each fraction. There was no evidence whether this meant multiple determinant groups in the same molecule or the presence of several different proteins in the fraction. This aspect is under further study, but for the present investigation the serums of patients showing such variable results were tested when possible on sites sensitized with serum from the same patient taken before treatment, to determine whether the patient had developed inhibiting antibody which blocked the particular antigenic groups to which he was sensitive. Where such a pretreatment serum from the same patient was not available, or did not satisfactorily sensitize skin sites to the fraction involved, the determination of the presence of blocking antibody was based on results obtained in tests against a number of different sensitizing serums.

IMMUNOLOGIC STUDY OF SERUMS FROM RABBITS INJECTED WITH FRACTION 1, FRACTION 2, AND WHOLE EXTRACT

(a) *Precipitins.*—Rabbits were injected with Fraction 1 and Fraction 2 from low ragweed pollen adsorbed on aluminum hydroxide by the method of Welker and Hektoen,[9] and other rabbits with a similar preparation of whole low ragweed pollen extract. A total of 30 to 35 ml. of each of these suspensions (approximately 10 mg. protein nitrogen) was injected intramuscularly in several sites. Trial bleedings were made at fourteen- to twenty-day intervals, and the serums were tested for precipitins with ragweed extract and the separate fractions. Animals showing a poor response or failing to respond were given two or more injections of the ragweed suspensions and were finally bled from the heart.

Precipitin tests were done by mixing 0.2 ml. of serum with equal amounts of the antigens (the concentrated antigens contained 0.5 mg. protein nitrogen per milliliter) in serial dilutions. The mixtures were heated at 37° C. in a water bath for one hour and then read after forty-eight hours in the ice box. In Table IV the highest dilution showing precipitins is recorded. A high titer specific precipitin content was obtained to Fraction 1 after two injections of Fraction 1 or whole extract, although three injections of Fraction 2 or whole extract produced a low titer of precipitins to this fraction in only one rabbit.*

(b) *Passive Transfer of Sensitivity to Guinea Pigs (Dale Test).*—Intraperitoneal injections of 2 to 3 ml. of the anti-ragweed rabbit serums were made into virgin guinea pigs. Forty-eight hours later, the uterine horns were removed, suspended in a bath of Tyrode's solution, and the presence of sensitivity to the fractions and whole extract determined by the consecutive addition to the bath of 0.3 mg. protein nitrogen of Fraction 2, Fraction 1, and whole extract. The specific contractions of the muscle caused by the addition of the antigens were recorded on a smoked drum. The results are summarized in Table IV. Rabbit serums showing precipitins to Fraction 1 transferred specific sensitivity to Fraction 1, and Fraction 1 neutralized to test with the whole extract, no transfer of sensitivity to Fraction 2 was obtained. In the previous experiments[1, 2] specific sensitivity to Fraction 2 as well as to Fraction 1 was obtained in guinea pigs actively sensitized with alum precipitated Fraction 1, Fraction 2, and whole extract.

(c) *Passive Sensitization of Human Skin.*—Five-hundredths of a milliliter of the rabbit serum were injected intracutaneously in triplicate sites in the skin of normal nonallergic test subjects. Forty-eight hours later these sites were tested with 0.025 ml. of a 0.01 mg. protein nitrogen per ml. (1,000 unit) dilution of Fraction 1, Fraction 2, and whole extract. The reactions were read at the end

*Since insufficient highly purified Fraction 2 remained for further injection in rabbits, low ragweed extract was adjusted to pH4, heated at 70° C. for one hour, the coagulated Fraction 1 removed, and after adjusting the pH to 7.2 the extract was concentrated by the cryochem apparatus and adsorbed on aluminum hydroxide. Rabbits 72, 82 and 83 were given two more injections of 35 ml. of this suspension. No precipitin response was obtained in rabbits 82 and 83, but rabbit 72 (after a total of 5 injections), showed precipitins to fraction 2 in a dilution of 1:80 and also to Fraction 1 in a dilution of 1:20, indicating this shortened method of preparing fraction 2 did not completely eliminate Fraction 1. Serum 72 passively sensitized the guinea pig uterus to both Fraction 2 and Fraction 1, but the sensitivity to Fraction 2 was dominant as this antigen neutralized the uterus to Fraction 1 and whole extract. Serum 72 did not passively sensitize human skin.

TABLE IV. IMMUNOLOGIC REACTIONS OF SERUM OF RABBITS INOCULATED WITH FRACTIONS 1 AND 2 AND WHOLE RAGWEED POLLEN EXTRACT

RABBIT NUMBER	INJECTED WITH FRACTION	NUMBER OF INJECTIONS	PRECIPITIN TITRE			PASSIVE SENSITIZATION OF GUINEA PIG (DALE TEST)		PASSIVE SENSITIZATION OF HUMAN SKIN TO TEST WITH		
			FRACTION		WHOLE RAGWEED	FRACTION		FRACTION		WHOLE RAGWEED
			1	2		1	2	1	2	
71	1	3	1:320	0	1:40	Positive	Negative	++	0	+
84	1	2	1:40	0				+	0	±
85	1	3	1:160	0	1:80	Positive	Negative	+	0	+
72	2	3	0	1:10				0	0	0
82	2	2	0	0		Negative	Negative			
83	2	2	0	0						
66, 67* 68	Whole Ragweed	2	1:160	0	1:80	Positive	Negative	+	0	0
55	Whole Ragweed	3	1:20	0	1:40	Negative	Negative	±	0	0

*Serums of rabbits 66, 67, and 68 pooled for tests.

of fifteen minutes and recorded in Table IV as 0 to ++ depending on the degree of reaction. Certain serums showing precipitins to Fraction 1 transferred specifically the skin reaction to this fraction. Serums acted more strongly to test to Fraction 1 than to test with whole extract, as might be expected since whole extract contains not more than 25 per cent of Fraction 1.

SUMMARY

1. Reaction of the Fraction 1 and Fraction 2 of low ragweed pollen with ragweed sensitive serums in passive transfer showed evidence of the independent specificity of the two fractions. With one serum Fraction 1 was 1,000 times as reactive as Fraction 2, while with another serum Fraction 2 was 100 times as reactive as Fraction 1.

2. Ragweed-sensitive patients treated with the separated fractions developed blocking antibody to the fraction injected but not to the other fraction.

3. Serums of rabbits injected with Fraction 1 showed specific reaction with this fraction in precipitin tests, passive sensitization of guinea pigs, and passive sensitization of human skin. Only one of three rabbits injected with Fraction 2 developed precipitins, but these were specific for Fraction 2.

4. Fraction 1 was a more active antigen than Fraction 2 both in man and rabbits.

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DISCUSSION

DR. ROBERT A. COOKE, (New York, N. Y.).—In spite of the developments of recent years with regard to antihistaminic drugs, I think we can all say that there is good reason to pursue the chemical and immunologic studies on pollens, because there is always going to be a field for their operation.

These immunochemical studies are really of twofold interest. The first, and I suppose foremost, is the ultimate practical application in therapy; and, secondly, they are of interest from a purely scientific angle for their value in furthering knowledge on the mechanics of immunologic reactions.

There are points of agreement, but very few. I think they can be summed up by saying that we all agree that pollens constitute a very complicated storehouse of varying chemical composition, containing several different antigenic substances. The second point on which we can agree is that the substances thus far found to be antigenic for animals or reactive for sensitized man have contained nitrogen. Perhaps we could also say that the material that is antigenic or reactive is colloidal in nature, although, there may be some disagreement on the size of the molecules.

But there is no agreement as to the chemical composition of the pollen antigens nor that they are protein, although in general the trend today favors the view that if they are not a complete protein molecule, at least they are some constituent of protein.

In Dr. Mosko's paper there are points that need clarification and further study, which, of course, will be given by him and his group. In the first place, the clinical groups that he has used are much too small, eight patients in most of them, the maximum was thirteen. A total of twenty-nine patients were tested with the antigenic fraction which he isolated.

The sensitivities of his patients to the nitrogen standardized extract by the relatively gross direct skin test were not reported. He says that extract A was highly reactive in skin test and yet could be given in almost any dose. If one examines the table which was his basis for this statement, one finds that the maximum dose—let us take extract A—ever used after many injections, was 0.06 mg. of nitrogen or less than 6000 protein nitrogen units of a regular extract, and this certainly is, at least as far as our types of treatment are concerned, a very small dose on which to assert safety from constitutional reactions with a heat-stable fraction.

He also states that this extract is nonantigenic for animals on the basis of gross anaphylaxsis, which is a comparatively rough method of determination in contrast to the much more sensitive Dale test. I think in experiments of this kind one should attempt to use the most delicate and accurate tests that have been devised.

Almost everything that he says about this fraction could be said equally about the Fraction 2 isolated by Stull in our studies at the Roosevelt Hospital; its heat stability, its low antigenicity, and its low capacity for inducing constitutional reactions in man except in the higher levels of dosage. This Fraction 2, when first isolated by Stull, was found low in protein and high in carbohydrate, but further purification raised the nitrogen and reduced the reducing substances.

Before discussing the studies of Baldwin and his group, I would like to say that I think it is a mistake to speak of or introduce into the literature the terms "Fractions 1, 2, and 3," and so forth, because it is going to be extremely difficult in future study of the literature to determine whether it is Baldwin's Fraction 1 or Stull's Fraction 1. I hope that perhaps an effort may be made to introduce a different nomenclature to avoid such confusion.

These studies of Baldwin and co-workers, however, are extremely interesting, for they have taken a rather different chemical approach with alcohol precipitation and used experimental animals rather than the sensitive human being as the indicator of reactivity.

It is significant, though, that these workers have found, as most of us have in the past, that chemical manipulation tends to denature the resulting fractions.

Dr. Sherman's presentation summarizes very well the extensive chemical and immunological studies made by him and by Stull over the years prior to their entrance into military service. By several immunologic technics, there seems to be good evidence that the designated Fraction 1 and Fraction 2 belong chemically in the classification of albumin and proteose; that they have independent antigenic activities; that they are both active in pollen sensitive patients, but definitely in different degrees.

The point that Dr. Sherman has made and which should be emphasized is that Fraction 2, though not very active in direct test or even on passive transfer test, will give a positive reaction in the skin of most but not all ragweed sensitive patients, if used in sufficient concentration, say 1000 units.

The subject of the chemistry of antigens and especially pollen antigens, is getting to be a very confusing one. In order to correlate the various data in the many laboratories, there are certain tests that appear indicated as basic for the determination of absolute activity of an allergen, or for the relative activity of two or more allergens, and as evidence for or against their immunologic identity.

These tests are; first, their activity in serial dilutions of active serum on passive transfer tests; second, the neutralization of sensitive human serum by passive transfer, as the direct test is a relatively crude and unsatisfactory test; and third, the neutralization of antigen by the blocking antibody in treated patients; and finally, the inactivation of the specially sensitized uterine horn in what is known as the Dale test, as the gross anaphylactic shock test is too unreliable.

By the combined use of such technics, the specificities and relative activities of any and all pollen extracts may be eventually evaluated and related.

To me it seems clear that if we are eventually to find that which we all wish, an ultimate solution of the problem of antigenicity in extracts for practical application and not just as an immunologic plaything, those in the Academy who are interested in these problems should, I think, develop a sort of informal cooperative group or body for discussion and for testing each other's products.

Coordinated scientific research showed what could be accomplished during the war, and we in the Academy would get further faster if we adopted a similar cooperative plan.

DR. WILLIAM B. SHERMAN (New York, N. Y.).—I have been very much interested in Dr. Mosko's and Dr. Baldwin's papers. I do think that it might help to get the different results together, to say that I feel reasonably sure that Dr. Mosko's fraction is very near to, if not identical with what we call Fraction 2. Dr. Stull, in trying to form a sort of short-cut method of making Fraction 2, happened to use almost exactly the same method of heating at pH 4 which Dr. Mosko used in preparing his fraction, and I must say the Fraction 2 prepared by that method was almost identical with that obtained by ammonium sulfate fraction. It contained traces of Fraction 1, and when guinea pigs or rabbits were sensitized with this preparation, an antibody was formed not only to Fraction 2, but also to Fraction 1.

CHEMICAL AND IMMUNOLOGIC STUDIES OF LOW RAGWEED POLLEN EXTRACT*†‡

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of H. Brown and K. J. Winfield, Jr.

THE present study is concerned with chemical fractionation of low ragweed pollen extract and with immunologic reactions produced by these fractions. The chemical studies have aimed primarily at obtaining products with increasing ratios of carbohydrate to nitrogen, and the work has resolved itself into an investigation of the relative role of the different fractions in various immunologic phenomena.

This subject has been approached before with ragweed or other antigens but with different chemical techniques than those to be described. For instance, Sevag and Seastone[1] and Ferry and Levy,[2] using egg albumin polysaccharide, obtained conflicting results in sensitizing guinea pigs. With ragweed, Black[3] in 1931 isolated a substance which contained 55 per cent reducing sugar and 6 per cent nitrogen and reported positive skin tests in sensitive persons in higher dilutions than with crude pollen extract. A carbohydrate fraction prepared by Johnson and Rappaport[4] was found to be relatively inert clinically. Caulfeild, Brown, and Waters[5] obtained a carbohydrate fraction containing 1.5 per cent nitrogen and 80 per cent reducing sugar and cross neutralization tests, indicated that it was antigenically different from other fractions of ragweed pollen. Fraction II of Stull, Sherman, and Hampton[6] contained carbohydrate and was active in skin tests of some sensitive patients but less effective in skin tests of other sensitive patients than their fraction I which did not contain carbohydrate.[6a] Newell[7] has reviewed the chemical studies on the allergens in pollens.

The antigenic effect of pollen extract in animals was studied by Clock[8] who found that precipitins and complement fixing antibodies could be produced in rabbits against ragweed pollen extracts. His results have been confirmed,[9-13] but the antibody response frequently has been irregular and weak. More recently, Eagle, Arbesman, and Winkenwerder[14] injected rabbits with ragweed pollen extract and obtained precipitative and complement fixing antibodies regularly in high titer.

Sensitization of rabbits and guinea pigs to ragweed was successfully accomplished by Harrison in 1934,[15] and his work has been repeated.[5, 16-18] In man, Cooke, Loveless, and Stull[19] have shown that two antibodies related to the same pollen extract are present in the serum of treated hay fever patients. These antibodies can be detected by the method of passive transfer. Thermostable antibodies have also been found by means of the precipitin reaction.[20, 21]

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To obtain additional information concerning the antigenic properties of low ragweed pollen extract and of some of its alcohol precipitable fractions, especially of those composed chiefly of carbohydrates, we have studied: (a) the ability of low ragweed pollen extract and of some of its fractions to induce precipitin formation in rabbits and guinea pigs; (b) the presence of precipitins for ragweed pollen extract and for these fractions in the sera of untreated and of treated ragweed-sensitive persons; (c) the ability of ragweed pollen extract and of these fractions to sensitize animals to the homologous and heterologous antigens; and (d) the threshold of sensitivity of skin and conjunctiva of untreated ragweed-sensitive persons to ragweed and to these fractions.

MATERIAL AND METHODS

(1) *Fractionation.*—Serial alcohol precipitation of aqueous low ragweed pollen extract was the method used. This was followed by chloroform treatment, suggested by Sevag[22] to be a relatively mild method of separating proteins from carbohydrate. Several series of precipitations were made. Following is a typical experiment: 50 Gm. of defatted low ragweed pollen were extracted for ten minutes with 300 c.c. of distilled water. This was repeated three times, and the four extractions combined to make a total of 1,200 c.c. of extract. This extract was concentrated in vacuo (water pump pressure) at 20° to 30° C. to 200 c.c. To this concentrated material was added slowly one volume of 95 per cent ethanol, at 10° C. The material was placed in a cold room at 10° C. for twenty-four hours. The precipitate was then separated by centrifugation in a bucket type centrifuge at 2,000 to 3,000 r.p.m. The soluble portion of this precipitate was dissolved in 200 c.c. of distilled water. This solution was called fraction I. To the supernatant fluid from the alcohol precipitate was added another volume of 95 per cent ethanol, and the same procedure followed as in the first precipitation. The soluble portion of the second precipitate was called fraction II. Similarly, fractions III, IV, V, and VI were obtained. It was necessary to keep the material in a cold room for several days in order to obtain the precipitate from which fractions IV, V, and VI resulted. The composition of the fractions obtained in a typical experiment is presented in Table I.

TABLE I. COMPOSITION OF FRACTIONS OF LOW RAGWEED POLLEN EXTRACT OBTAINED BY SERIAL ALCOHOL PRECIPITATION, FOLLOWED BY CHLOROFORM TREATMENT

FRACTION	VOLUME OF ALCOHOL	TOTAL NITROGEN (TN U/C.C.)	CARBOHYDRATES BEFORE HYDROLYSIS MG./C.C.	CARBOHYDRATES AFTER HYDROLYSIS MG./C.C.	INCREASE WITH HYDROLYSIS	RATIO TN/CHO
WLR*	0	50,000	2.0	3.0	1.5	.16
I	1	10,500	0.234	0.504	2	.21
II	2	9,000	0.125	0.447	3	.22
III	3	6,600	0.065	0.349	5	.22
IV	4	19,700	0.225	2.625	10	.076
V	5	5,900	0.055	0.594	11	.10
VI	6	2,700	0.0145	0.069	5	.40

*WLR means whole low ragweed.

Fractions I, II, and III were similar in their ratios of nitrogen to carbohydrate; therefore, it was decided to use a fraction similar to II for immunologic studies as a representative of this group, and a fraction similar to IV as an example of a dissimilar group. In order to obtain a carbohydrate fraction containing less nitrogen, fraction IV was further fractionated. To the 200 c.c. of material was added 20 to 30 c.c. of chloroform, and the mixture was vigorously shaken by hand for thirty minutes. It was then centrifuged in a bucket type centrifuge at 2,000 r.p.m. for thirty minutes. At the end of this time three separate layers formed. At the bottom was a clear chloroform layer. At the top was a clear aqueous layer. The middle layer was a turbid emulsion of chloroform, water, and precipitated material. The top aqueous layer was drawn off and similarly treated with chloroform. The process was repeated until no precipitate formed at the chloroform-water interface. This usually required nine to ten treatments. The final aqueous layer was concentrated to 100 c.c., and sodium acetate was added to saturation. The mixture was then chilled and 250 c.c. of chilled 95 per cent ethanol were added. The solution was kept for three days in a cold room, the precipitate removed by centrifugation, and the precipitate dissolved in 200 c.c. of distilled water. This final fraction was called fraction S, and was used for immunologic studies.

In other experiments the water extract of the defatted pollen was not concentrated before precipitation. From such an experiment fraction B, similar to fraction II, was obtained. This material was used for immunologic studies without chloroform treatment, while fraction D, similar to fraction IV, from the same experiment was treated with chloroform before it was used for immunologic studies. The relative amounts of nitrogen and reducing material calculated as glucose are shown in Table II.

TABLE II. COMPOSITION OF FRACTIONS OF LOW RAGWEED POLLEN EXTRACT USED FOR IMMUNOLOGICAL STUDIES

FRACTION	CHEMICAL COMPOSITION			
	PER CENT N	PER CENT CARBOHYDRATE	INCREASE WITH HYDROLYSIS	SOLIDS MG./C.C.
WLR	5	30	1.5	10.0
B	7	14	4	0.72
D	4.9	58	22	1.0
S	1.4	60	52	1.67

It is to be noted that the percentage of nitrogen decreased from B to D to S, and that the amount of total carbohydrate increased in that order. The increase in reducing value on hydrolysis of the fractions was in the same direction, which is evidence that a more nearly pure polysaccharide is obtained.

It will be seen that there was a large amount of reducing material in whole ragweed extract, but very little increase upon hydrolysis, which indicates that the amount of polysaccharide was small as compared to other reducing substances.

The amounts of total solid of fractions B, D, and S were less than those of whole ragweed extract; fraction S gave a negative ninhydrin test. This

effect was qualitative because the other fractions, diluted to contain per cubic centimeter the same amount of nitrogen as the dilution of fraction S, gave a positive ninhydrin test.

Nitrogen determinations were done by the micro-Kjeldahl technique, the distillate was nesslerized and estimated in a Klett-Summerson photoelectric colorimeter. The carbohydrate determinations were done by the method of Folin-Wu, and were measured in a Klett-Summerson photoelectric colorimeter. The samples were hydrolyzed for ninety minutes at 100° C. in 1 N/sulfuric acid.

2. *Immunologic Studies.*—

Animals: Thirty healthy, albino, male rabbits, weighing 2,500 to 3,000 Gm. and 30 healthy, albino guinea pigs weighing 250 to 300 Gm. were used.*

Human Beings: Sera from seven untreated and from ten treated ragweed-sensitive patients were tested for precipitins for ragweed pollen extract and its fractions. Tests for threshold reaction of skin and conjunctiva to ragweed and its fractions were done on 15 untreated ragweed-sensitive persons.

Antigens: The low ragweed pollen extract was prepared in the usual way, by extraction of 5 Gm. of dry pollen for twenty-four hours in 100 c.c. of Coca's fluid. It contained approximately 0.52 mg. N per c.c. (= 52,000 T N units). The preparation of the various fractions and their chemical composition has already been described in this communication.

Production of Precipitative Antisera.—Rabbits were given 16 to 20 intravenous injections of ragweed pollen extract or 12 intravenous injections of its fractions. Increasing amounts of the antigens were injected three times a week, according to the method of Eagle and co-workers.[14] The ragweed pollen extract injected into each rabbit contained a total of approximately 40 to 60 mg. N, while approximately 4 mg. N were present in the total amount of fractions B and D given to each animal.

Guinea pigs received six intradermal injections of 0.1 c.c. amounts of the same antigens over a period of twelve days, as suggested by Chase.[23] Expressed in nitrogen, a total of approximately 0.3 mg. of ragweed pollen extract, or of approximately 0.03 mg. of the two fractions were injected.

Precipitin Tests.—Sera of untreated rabbits, guinea pigs and ragweed—sensitive human beings, as well as sera obtained after intravenous or intradermal immunization, were tested against ragweed pollen extract and its fractions. Two methods were used. The "Ring Test" was performed as follows: 0.3 c.c. quantities of the undiluted sera were introduced with a capillary pipette into a series of tubes containing 0.3 c.c. quantities of undiluted, and of diluted (1:2; 1:5; 1:10; 1:25) antigen. Physiologic saline solution was used for dilution. The tubes were kept at room temperature and readings made after fifteen minutes, one, and two hours. A white ring at the interface between antigen and sera was considered evidence for the presence of precipitative antibodies and the result recorded as "positive." Absence of the ring was recorded as "negative." The "Mix Test" was performed by mixing undiluted antigen with various serum dilutions, according to the method described by Eagle and

*Through the courtesy of Dr. M. W. Chase of the Rockefeller Institute for Medical Research we obtained four guinea pigs that had previously been given sensitizing injections of pollen extract (one animal), or of alum-precipitated pollen extract (three animals).

associates.[14] The mixtures were kept at 37° C. for four hours, and overnight at room temperature. Turbid mixtures were considered as evidence for the presence of precipitins and recorded as "positive"; mixtures remaining clear were recorded as "negative." The results obtained with both methods were practically identical.

In Vivo Tests.—Skin tests in rabbits and guinea pigs were performed at various intervals after intravenous or intradermal introduction of pollen extract or of its fractions, using 0.1 c.c. quantities of the homologous and of heterologous antigens.

In man, the threshold of sensitivity to ragweed extract and to its fractions was determined for skin and conjunctiva according to the method of Loveless.[24]

RESULTS

Studies With Precipitative Antisera.—Precipitative antibodies for the homologous antigen were obtained in all 15 rabbits that had been given intravenous injections of ragweed pollen extract. A "low" titer (1:1.25 or less) was found in 4, a "medium" titer (1:2.5) in 4, and a "high" titer (1:5 to 1:20) in seven.

Precipitative antibodies for the homologous antigen were also obtained in all five rabbits that had been given intravenous injections of fraction B, while none of 5 rabbits injected intravenously with fraction D produced precipitins against this fraction or against the heterologous antigens. Thus, fraction D was not antigenic in this experiment.

Aside from antibodies against the homologous antigens, precipitins could also be detected against heterologous antigens in antiragweed and in anti-fraction B sera. A typical experiment is presented in Table III.

TABLE III. PRECIPITIN TESTS BETWEEN RABBIT ANTISERA AGAINST RAGWEED OR AGAINST ITS FRACTIONS, AND HOMOLOGOUS AND HETEROLOGOUS ANTIGENS*

	ANTISERUM AGAINST			CONTROLS	
ANTIGEN	RAGWEED POLLEN EXTRACT	FRACTION B	FRACTION D	NORMAL RABBIT SERUM	SALINE
Ragweed pollen extract	+++	++	0	0	0
Fraction B	++	+	0	0	0
Fraction D	+	±	0	0	0
Fraction S	0	0	0	0	0
Saline Control	0	0	0	0	

*No antiserum against fraction S was available.
Key: 0 means negative; ± to +++ means varying degrees of precipitation.

No precipitins against homologous or heterologous antigens were detected in the sera of eight guinea pigs injected intradermally with ragweed pollen extract, or with its fractions.

No precipitins against ragweed pollen extract or its fractions were found in the sera of seven untreated ragweed-sensitive persons, nor in those of 10 patients who had been given subcutaneous injections of ragweed pollen extract over periods ranging from a few months to several years.

In Vivo Studies.—Skin tests with ragweed pollen extract and the various fractions were done on 20 guinea pigs eleven to thirty-five days after the last

of six intradermal injections of the various antigens. Marked reactions were obtained with tests performed after eighteen and after twenty-five days. It will be seen from Table IV that, regardless of the antigen used, sensitization to the whole ragweed extract was obtained. Sensitization to fraction B was produced with whole ragweed and with fractions B and D. Sensitization to fraction D was produced only with this fraction. No sensitization to fraction S by any of the materials could be obtained. It is interesting to note that whereas fraction S did not elicit any reaction in sensitized animals it did sensitize animals against the whole ragweed extract.

TABLE IV. SKIN TESTS IN GUINEA PIGS SENSITIZED WITH RAGWEED POLLEN EXTRACT OR ITS FRACTIONS

ANTIGEN USED FOR SENSITIZATION	ANTIGEN USED FOR SKIN TESTS			
	RAGWEED POLLEN EXTRACT	FRACTION B	FRACTION D	FRACTION S
Ragweed pollen extract	+	+	0	0
Fraction B	+	±	0	0
Fraction D	+	+	±	0
Fraction S	+	0	0	0

Key: 0 means no reaction; ± means slight hyperemia; + means hyperemia measuring 5 to 10 mm. in diameter.

Skin tests were also performed on rabbits injected intravenously with ragweed pollen extract. Most animals were found to be sensitive to ragweed in tests made eleven to one hundred ten days following injection. Studies with the various fractions were not carried out at this time.

The threshold of sensitivity to ragweed and the various fractions were determined quantitatively for skin and conjunctiva in 15 untreated ragweed sensitive human beings. The technique of Loveless[24] was used. It was found that the low ragweed extract had a lower threshold than fraction B which likewise was more reactive than fraction D, while fraction S was the least reactive of all. This relationship was noted in all the subjects tested. The figures observed in the individual tests were done on a comparatively small group and showed considerable variations. It should be emphasized, however, that fraction S elicited positive reactions in the skin and conjunctiva of untreated ragweed sensitive patients.

DISCUSSION

This work was undertaken with the hope that in the field of atopic sensitivity, a study of ragweed might reveal some immunologic specificity of the nitrogen or of the carbohydrate (polysaccharide) fraction similar to that shown by Heidelberger, Avery and Goebel[25] and others for bacteria. Certainly no such clear-cut results were obtained in this study.

Certain interesting phenomena, however, were observed. We found as did Eagle and his associates[14] that intravenous injections of whole low ragweed pollen extract into rabbits are followed regularly by the appearance of precipitative antibodies. Fraction B also elicited precipitins in all rabbits. The total nitrogen injected with this fraction was only approximately one-tenth

of the amount injected with the whole ragweed. With fraction D containing the same amount of total nitrogen as B, but a much higher amount of carbohydrate (58 per cent, as compared with 14 per cent) no precipitins were obtained. It is possible that the high carbohydrate content in fraction D interfered with the production of precipitative antibodies. Such an assumption as far as it concerns precipitin formation in rabbits would go further than the one reached by Unger and associates,[13] who stated that the allergen in ragweed is protein in nature and that the polysaccharide plays no part in the specific activity. However, the absence of demonstrable antigenic activity, as shown by the inability to produce precipitins, does not necessarily mean that the carbohydrate fraction may not elicit antibodies in other species. Francis and Tillett[26] using polysaccharide of pneumococcus Type I found that antibody formation was demonstrable when it was injected into man, but not when given to rabbits.

Sensitization of rabbits to low ragweed pollen extract, already noted by previous investigators, was also obtained in this study. Intradermal injections into guinea pigs with ragweed extract, as well as with its fractions, rendered this species sensitive to whole ragweed pollen extract and also to the homologous fraction. This was observed even with a purified carbohydrate (fraction D). It would, therefore, appear that these fractions are not entirely devoid of antigenic activity, although they fail to induce precipitin formation in rabbits.

Similarly, the studies on the threshold of sensitivity of ragweed and of its fraction for skin and conjunctiva of untreated ragweed sensitive persons showed that fractions with a low nitrogen and high carbohydrate content were able to elicit reactions. However, these reactions were considerably weaker than those obtained in the same test subject with whole low ragweed pollen extract, and were approximately proportional to the N content of the materials tested.

Several investigators have shown that patients sensitive to ragweed may vary in their response to various fractions of ragweed extract, i.e., one patient may be more sensitive to one fraction than to another, while the reverse may be true of a second patient. Sherman and Hebald[6a] observed that patients more sensitive to fraction II of Stull, Sherman, and Hampton[6] are more likely to undergo constitutional reactions during treatment with whole ragweed pollen extract. Whether a specific treatment should make use of those fractions of ragweed to which the patients are particularly sensitive is an important question for investigation. By the same token it is equally important to investigate fractions to which no sensitivity may be demonstrable. Certainly in view of the work of Rich[27] and others there is considerable question as to whether the phenomena of hypersensitivity and immunity necessarily go hand in hand and are essential one to the other. In the effort to separate ragweed pollen into its specific fractions, the use of several species for testing the materials obtained, is desirable. The work reported here was designed as the beginning of a program to study the effects of fractions in more than one species. It is obvious that only a beginning has been made and that a sustained effort is necessary for the achievement of the results. It is felt that fraction S is most interesting because it did produce sensitivity in guinea pigs, and it seems to be qualitatively different from the other fractions used.

As one reviews this work three phases of the results are most suggestive and interesting. In the first place, the more we attempted to purify and fractionate the original extract the less striking and consistent were the immunologic reactions observed. In the second place, in general, immunologic reactivity diminished with a decrease in the nitrogen content of the fraction. However, third and finally, a carbohydrate fraction with a negative ninhydrin reaction did sensitize guinea pigs to whole ragweed extract although in itself was unable to elicit positive skin reaction in sensitized animals; however, this same fraction did give positive skin tests in untreated humans sensitive to ragweed. The possibility that the relatively small amount of antigenicity exhibited by fraction S is due to a protein contaminant cannot be excluded, since it is possible that it contains an amount of protein too small to be detected by the ninhydrin test.

In spite of the vast amount of chemical and immunologic investigation of antigens in atopic sensitivity the results are still conflicting, inconclusive and from a practical clinical standpoint, disappointing. It is, however, a fascinating field of investigation that may hold ultimately the solution of immunizing sensitive individuals more effectively without the danger of constitutional reaction.

SUMMARY

1. The immunologic activity of three fractions of low ragweed pollen extract, prepared by serial precipitation with alcohol and treatment with chloroform was compared with that of standard pollen extract.

2. Fraction B contained approximately 7 per cent nitrogen and 14 per cent carbohydrate; fraction D contained approximately 5 per cent nitrogen and 58 per cent carbohydrate, and fraction S contained approximately 1.4 per cent nitrogen and 60 per cent carbohydrate and gave a negative ninhydrin test.

3. Standard pollen extract and fractions B and D, but not fraction S were precipitated in vitro by rabbit anti-ragweed serum. Standard pollen extract and fraction B, but not the others, were also precipitated by rabbit anti-fraction B serum. No precipitations were observed with rabbit anti-fraction D serum.

4. Sensitization of guinea pigs to standard pollen extract was produced with each fraction. Sensitization to fraction B was produced with all fractions, except fraction S. Sensitization to fraction D was produced only with fraction D. No sensitization to fraction S could be produced.

5. Studies of untreated ragweed sensitive persons showed that the threshold of sensitivity for skin and conjunctiva to standard pollen extract was lower than to any of the three fractions.

6. Fairly strong evidence is presented indicating that the carbohydrate fraction of low ragweed pollen extract is not a very active antigen since, while it sensitized guinea pigs to whole ragweed extract and elicited positive reactions in untreated ragweed sensitive human beings, it failed to produce precipitins in rabbits.

7. The further the attempts to purify and fractionate the original ragweed pollen extract were carried out, the less striking and consistent were the immunologic reactions observed. Immunologic reactivity diminished with a decrease in the nitrogen content of the fraction.

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SKIN TESTS IN DOGS WITH COMMON ALLERGENS*†

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WITTICH[1] in 1941 obtained positive skin reactions to ragweed antigen in a dog with typical clinical symptoms of hay fever. Passive transfers of the cutaneous sensitivity to dog and man were successful. A systemic reaction followed the intracutaneous tests in the dog and consisted of vomiting, scratching of the body and nose, lacrimation of the eyes, and generalized urticaria.

Brunner, Altman, and Bowman,[2] in 1944, reported positive skin reactions to canine and pig ascaris extracts in dogs with nematode infestations. Positive transfer of the skin sensitizing antibodies in the blood serum to normal dogs and humans were successfully demonstrated. Active sensitization of two normal dogs with ascaris extract was likewise successful. Constitutional reactions occurred in two dogs following intracutaneous tests with ascaris antigen.

Moreno and Bentolila,[3] in 1945, obtained positive skin reactions in a dog to corn, oats, cocoa, and dust; and described the occurrence of spontaneous allergy in this animal. Following these tests a generalized reaction characterized by pruritis, erythema, and dyspnea appeared and was controlled by injections of epinephrine. Passive transfer of the positive cutaneous reactions to a normal dog was successful.

Hence, there is sufficient evidence to indicate that reaginic allergy is a canine problem as well as a human one. The writers, therefore, decided to study a series of unselected animals for evidences of allergy.

Sixteen dogs ranging from 4 months to 12 years of age were tested with a series of inhalant and food allergens; each dog was shaved on the anterior part of the abdomen which was found to be the most suitable area for the cutaneous tests. Testing was done after an interval of two or more days when all of the irritation of the skin caused by shaving had subsided.

The allergens used were those most commonly employed in the routine testing of humans, but the concentrations of the extracts were stronger. The allergens in terms of total nitrogen content or stock dilutions included the following inhalants and foods: house dust, undiluted; feathers, 0.1 mg. nitrogen per ml.; wool, 0.1; goat hair, 0.1; cottonseed, 0.01; orris, 1:10; ragweed, 0.1; timothy, 0.1; flaxseed, 0.01; cat epithelia, 0.1; dog epithelia, 0.1; pyrethrum, 1:100; tobacco, 1:10 dilution; and yeast, 1:10 dilution.

*From the Division of Allergy of the Jewish Hospital of Brooklyn, New York.

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The foods tested included chocolate, 0.025; egg, 0.001; chicken 0.1; herring, 0.001; glue, 0.01; beef, 0.05; soy bean, 0.01; corn, 1:10; peanut, 0.005; milk, 1:10; wheat, 1:10; and oat, 1:10.

Ascaris extract 0.1 was also used for routine testing.

About 0.05 ml. of the allergen was introduced into each skin site.

A positive skin test consisted of a wheal in the form of an edematous area having a pinkish hue without any surrounding erythema. The wheal was round and was accompanied at times by pseudopods during the development of the reaction. No pruritis was noted to be associated with these reactions. The positive test reached its maximum size at the end of twenty-five minutes at which time readings were made.

TABLE I A. CUTANEOUS REACTIONS IN DOGS WITH COMMON ALLERGENS

NUMBER	1	2	3	4		1	2	3	4
SEX	F	M	M	M		F	M	M	M
AGE	OLD	OLD	OLD	OLD		OLD	OLD	OLD	OLD
INHALANTS					FOODS				
Dust (undil.)	+++	0	+±	++±	Wheat 1:10	0	0	0	0
Feathers 0.1	+++	0	0	0	Chocolate 0.025	0	0	0	0
Wool 0.1	±	0	0	0	Egg 0.001	0	0	0	0
Cow Epithelium 0.1	0	0	0	0	Chicken 0.01	0	0	0	0
Goat Epithelium 0.1	++	0	++±	+±	Herring 0.001	0	0	0	0
Pyrethrum 1:100	++	0	0	0	Milk 1:10	0	0	0	0
Tobacco 1:10	±	0	0	±	Beef 0.05	0	0	0	0
Cottonseed 0.01	±	0	0	0	Oats 1:10	0	0	0	0
Orris 1:10	+	0	0	0	Yeast 1:10	0	0	0	0
Ragweed 0.1	0	0	0	0	Soy Bean 0.01	0	0	0	0
Timothy 0.1	0	0	0	0	Corn 1:10	0	0	0	0
Cat Epithelium 0.01	0	0	0	0	Peanut 0.005	0	0	0	0
Dog Epithelium 0.01	0	0	0	0					
Horse Epithelium 0.01	0	0	0	0	Ascaris 0.1	+++	+++		
Rabbit Epithelium 0.01	0	0	0	0					
Glue 0.01	0	0	0	0					
Flaxseed 0.01	0	0	0	0					

Single numbers = dilutions in terms of milligrams nitrogen per cubic centimeter.
Ratios = dilutions of stock extracts.

TABLE I B. CUTANEOUS REACTIONS IN DOGS WITH COMMON ALLERGENS

NUMBER	5	6	7	8		5	6	7	8
SEX	F	M	M	M		F	M	M	M
AGE	5 MO.	4 MO.	4 MO.	10 YR.		5 MO.	4 MO.	4 MO.	10 YR.
INHALANTS					FOODS				
Dust (undil.)	0	0	0	0	Wheat 1:10	0	0	0	0
Feathers 0.1	0	0	0	0	Chocolate 0.025				
Wool 0.1					Egg 0.001	0	0	0	0
Cow Epithelium 0.1	0	0	0	0	Chicken 0.1				
Goat Epithelium 0.1	0	0	0	0	Herring 0.001	0	0	0	0
Pyrethrum 1:100	0	0	0	0	Milk 1:10	0	0	0	0
Tobacco 1:10	0	0	0	0	Beef 0.05	0	0	0	0
Cottonseed 0.01					Oats 1:10	0	0	0	0
Orris 1:10	0	0	0	0	Yeast 1:10	0	0	0	0
Ragweed 0.1	0	0	0	0	Soy Bean 0.01	0	0	0	0
Timothy 0.1	0	0	0	0	Corn 1:10	0	0	0	0
Cat Epithelium 0.01					Peanut 0.005	0	0	0	0
Dog Epithelium 0.01									
Horse Epithelium 0.01					Ascaris	++	+++	+++	+±
Rabbit Epithelium 0.01									
Glue 0.01									
Flaxseed 0.01									

Tests were reported according to the size of the wheal (mm. of the diameter).

o	negative	
±	negative slight	4 mm. in diameter
+	slight	5 mm. in diameter
+±	slight moderate	6 mm. in diameter
++	moderate	7 mm. in diameter
++±	moderate marked	7-8 mm. in diameter
+++	marked	9-10 mm. in diameter or more.

The results of all tests are tabulated in Table I. The number of positive and doubtful reactions obtained with various allergens are listed in Table II.

TABLE I C. CUTANEOUS REACTIONS IN DOGS WITH COMMON ALLERGENS

NUMBER	9	10	11	12		9	10	11	12
SEX	F	M	M	F		F	M	M	F
AGE	2 YR.	12 YR.	5 YR.	8 YR.		2 YR.	12 YR.	5 YR.	8 YR.
INHALANTS					FOODS				
Dust (undil.)	+±	+++	+++	+	Wheat 1:10	0	+	0	+++
Feathers 0.1	0	++±	0	0	Chocolate 0.025	0			0
Wool 0.1					Egg 0.001	0	0	0	+
Cow Epithelium 0.1	0	++	0	0	Chicken 0.1	0			
Goat Epithelium 0.1	+	0	+	0	Herring 0.001	0	0	0	0
Pyrethrum 1:100	0	0	0	0	Milk 1:10	0	0	0	+++
Tobacco 1:10	0	±	0	0	Beef 0.025	0	0	0	0
Cottonseed 0.01					Oats 1:10	0	0	0	0
Orris 1:10	0	±	0	0	Yeast 1:10	0	0	0	0
Ragweed 0.1	0	+	0	0	Soy Bean 1:10	0	+	0	0
Timothy 0.1	0	0	0	0	Corn 1:10	0	0	0	0
Cat Epithelium 0.01					Peanut 0.005	0	0	0	±
Dog Epithelium 0.01									
Horse Epithelium 0.01					Ascaris 0.1	+±	++	+++	+
Rabbit Epithelium 0.01									
Glue 0.01									
Flaxseed 0.01									

TABLE I D. CUTANEOUS REACTIONS IN DOGS WITH COMMON ALLERGENS

NUMBER	13	14	15	16		13	14	15	16
SEX	M	M	M	F		M	M	M	F
AGE	3 YR.	4 YR.	3 YR.	4 YR.		3 YR.	4 YR.	3 YR.	4 YR.
INHALANTS					FOODS				
Dust (undil.)	+++	++±	++±	+++	Wheat 1:10	0	0	0	0
Feathers 0.1				++	Chocolate 0.025	0	0	0	0
Wool 0.1				±	Eggs 0.001	0	0	0	0
Cow Epithelium 0.1				±	Chicken 0.1	0	0	0	0
Goat Epithelium 0.1				+±	Herring 0.001	0	0	0	0
Pyrethrum				0	Milk 1:10	0	0	0	0
Tobacco 1:10				0	Beef 0.05	0	0	0	0
Cottonseed 0.01				0	Oats 1:10	0	0	0	0
Orris 1:10				0	Yeast 1:10	0	0	0	0
Ragweed 0.1				0	Soy Bean 1:10	0	0	0	0
Timothy 0.1				0	Corn 1:10	0	0	0	0
Cat Epithelia 0.01				0	Peanut 0.005	0	0	0	0
Dog Epithelia 0.01				0					
Horse Epithelia 0.01				0	Ascaris 0.1	++	++±	+++	+++
Rabbit Epithelia 0.01				0					
Glue 0.01				0					
Flaxseed 0.01				0					

TABLE II. SUMMARY OF POSITIVE REACTIONS TO COMMON ALLERGENS

ALLERGEN	NUMBER OF DOGS TESTED	POSITIVE REACTIONS + TO +++		DOUBTFUL REACTIONS ±	
*Ascaris 0.1	14	14	(100%)		
Dust (undiluted)	16	11	(68%)		
Goat Epithelia 0.1	13	7	(53%)		
Wool 0.1	5	0		2	(40%)
Feathers 0.1	13	3	(23%)		
†Tobacco 1:10	13	0		3	(23%)
Cottonseed 0.01	5	0		1	(20%)
Cow Epithelium 0.1	13	1	(8%)	1	(8%)
Orris 1:10	13	1	(8%)	1	(8%)
Pyrethrum 1:100	13	1	(8%)		
Ragweed 0.1	13	1	(8%)		
Wheat 1:10	16	2	(12%)		
Milk 1:10	11	1	(9%)		
Soy Bean 0.01	14	1	(7%)		
Egg 0.001	16	1	(6%)		

*Dilutions indicated in mg. Nitrogen per ml.
†Dilutions of stock extract.

All 14 dogs tested with ascaris antigen containing 0.1 milligrams nitrogen per milliliter gave positive cutaneous reactions. Eleven (68 per cent) showed positive skin tests to foods or inhalants. Five showed no inhalant or food reactions. House dust antigens produced positive cutaneous reactions in eleven dogs.

It is to be noted that the inhalants produced more reactions than foods. Moreover, most of the inhalant reactions were strong. In only two dogs were reactions obtained to food allergens. None showed positive reactions to foods without positives to inhalants as well.

The three allergens which gave the highest number of positive reactions were ascaris extract (100 per cent), house dust (68 per cent), and goat epithelium (61 per cent).

Three dogs (No. 10, No. 1, and No. 16) gave six or more positive reactions. Dog No. 10 showed 11 positive reactions, 8 to inhalants, 2 to foods, and 1 to ascaris. Dog No. 1 showed 9 positive reactions, 8 to inhalants, and 1 to ascaris. Dog No. 16 showed 6 positive reactions, 5 to inhalants and 1 to ascaris.

Age was a factor, since the three youngest dogs between 4 and 5 months of age did not react to any of the inhalants or foods. However, they gave positive cutaneous reactions to ascaris antigens.

Dogs in which positive reactions occurred were studied for clinical manifestations. Dog No. 1 had paroxysmal attacks of sneezing whenever the home was swept. Cutaneous tests were positive to house dust, feathers, goat epithelium, pyrethrum, orris root, and ascaris. A study of the blood smear revealed a differential count of 88 neutrophiles, 8 lymphocytes, and 4 monocytes. Two nasal smears from each nostril showed no eosinophiles.

Dog No. 12, a short-haired fox terrier, had a dermatitis. The positive cutaneous reactions included wheat, egg, milk, and peanut. When these foods were eliminated from the diet, the skin cleared. Four months later the dog

was fed two slices of whole wheat, soy bean bread, and the dermatitis recurred. A return to rigid diet caused a subsidence of the dermatitis.

A series of passive transfer studies were done in order to determine whether the positive cutaneous reactions were based on a reaginic mechanism. Blood was obtained from dog No. 1 and the serum was prepared in the usual manner. Two dogs, No. 6 and No. 7, were selected as recipients because they both gave negative reactions to all inhalant and food allergens. Four cutaneous sites on dog No. 6 were injected with 0.1 ml. of serum of dog No. 1. Three days later these prepared sites were tested with several allergens and gave the following results: house dust +, feathers +, goat epithelium ++, pyrethrum 0. All control tests were completely negative. The results are noted in Table III.

TABLE III. PASSIVE TRANSFER TESTS WITH SERUM FROM DOG NO. 1

ALLERGEN	DIRECT TEST	PASSIVE TRANSFER TEST			
		RECIPIENT DOG NO. 6		DOG NO. 7	
		TEST	CONTROL	TEST	CONTROL
Dust (undiluted)	+++	+	0	+	0
		++	0	++	0
		+±	0	+	0
Feathers* 0.1	+++	+	0	+	0
Goat Epithelium 1:100	++	++	0	+	0
Pyrethrum† 1:100	++	0	0	0	0

*Milligrams nitrogen per milliliter.
†Stock dilution.

Four cutaneous sites on dog No. 7 were injected with 0.1 milliliters of serum from dog No. 1. Three days later the prepared sites were tested and gave the following results: house dust +, feathers +, goat epithelium +, and pyrethrum 0. Control tests were negative. These results are noted in Table III.

Two weeks later the same recipient dogs, No. 6 and No. 7, were each sensitized at two cutaneous sites with the serum of dog No. 1. House dust antigen was injected into these prepared cutaneous sites on each dog. All of the four sites tested gave positive reactions to house dust. Two were ++ one +±, and the other gave a + reaction. Control tests were negative. (Table III).

Summarizing the results, it will be seen that house dust gave a positive transfer reaction in six trials, feathers in two, and goat epithelium in two. Pyrethrum, however, failed to transfer on two trials. Attempts were made to sensitize a human with serum from dog No. 1. The marked local reactions which appeared at the prepared sites after the injection of serum rendered the interpretation of the results of transfer tests impossible.

SUMMARY

1. Sixteen dogs were tested intracutaneously with common inhalants, foods, and with ascaris extract.

2. Positive cutaneous reactions were obtained to house dust, feathers, goat epithelium, cow epithelium, orris ragweed, pyrethrum, tobacco, cottonseed, wheat, milk, and soy bean.

3. Passive transfer was accomplished with antigens of dust, feathers, goat epithelium, but failed with pyrethrum. Transfer tests with other antigens were not made.

4. In two dogs, one with positive reactions to inhalants, the other to foods, the positive reactions were found to be of clinical significance.

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PYRIBENZAMINE VERSUS SPECIFIC HYPOSENSITIZATION IN THE TREATMENT OF POLLINOSIS: A COMPARATIVE STUDY*†‡

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THE production of anaphylaxis and of some forms of allergy by histamine-like substances has been known for many years. This observation has led to the wide application of so-called antihistaminic drugs in the treatment of allergic conditions. Many investigators[1-15] in the past few years have studied the effects of these drugs and found them to be beneficial in the relief of symptoms of certain allergic conditions. Recently, Feinberg[16] reviewed the literature on this topic.

Arbesman, Koepf, and Lenzner[11] showed that one of these antihistaminic drugs, pyribenzamine, was of value in relieving the symptoms of 80 per cent of patients suffering from ragweed hay fever. Our present study compares the relative efficacy in allergic rhinitis due to ragweed pollen between the usual method of hyposensitization injections of pollen extracts and treatment with pyribenzamine.

In the early spring of 1946, alternate patients under pollen therapy in the Allergy Clinics of the Buffalo General and the Children's Hospitals were divided without selection into two groups. Group I was continued on injections of pollen and other extracts, such as dust and feathers. In addition, other palliative remedies (ephedrine, etc.) were prescribed when indicated. Group II was given injections of physiologic saline solution in place of the pollen extracts, plus other nonseasonal extracts, but no other medicine was prescribed except pyribenzamine.

The difficulty is fully realized in evaluating the results of therapy in so variable a condition as pollinosis, using subjective symptoms alone as an index. An attempt was made, therefore, to be as critical as possible in analyzing results.

METHODS

The patients in both groups were given the usual daily symptom cards and instructed as to their use. Each time the patient was seen a note was made on the outpatient chart describing the status of his hay fever and asthma since the previous visit.

Another study using the same methods of evaluation was done in private practice, comparing results with the usual intradermal coseasonal therapy plus

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†The Pyribenzamine was furnished through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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symptomatic drugs with the results in a similar group receiving pyribenzamine alone.

At the end of the 1946 ragweed pollen season, the outpatient charts and the patients' symptom cards were reviewed by each of the three authors independently. The average degree of relief of each of these individual estimations was then recorded. It is interesting to note that, despite the lack of an accurate measuring stick to evaluate the results of treatment, the ratings of these patients by each of the three authors were very similar.

Those patients who received 50 per cent or more relief of symptoms were classified as improved.

TABLE I. HAY FEVER—RAGWEED

TREATMENT	CLINIC		PRIVATE PRACTICE	
	CASES NUMBER	IMPROVED PER CENT	CASES NUMBER	IMPROVED PER CENT
Pyribenzamine only	32	66	22	82
Preseasonal injections plus usual drugs	27	67		
Coseasonal injections plus usual drugs			10	60

RESULTS

A. Ragweed Hay Fever.—(Table I) Fifty-nine patients in the clinics with ragweed hay fever were considered suitable for a comparative study. There were more than 59 patients in this group at the beginning of the study, but, because of various factors such as insufficient treatment (only those patients receiving adequate hyposensitization therapy were used) and other dominant allergies, many had to be excluded.

Thirty-two of these 59 patients were treated with pyribenzamine alone and improvement was noted in 66 per cent. The remaining 27 patients on pollen injection therapy plus other symptomatic drugs showed relief of symptoms in 67 per cent. Of the coseasonal cases, 82 per cent of 22 patients treated with only pyribenzamine in private practice were improved and six out of ten on intradermal injections plus palliative therapy were benefited.

TABLE II. ASTHMA-RAGWEED

TREATMENT	CLINIC		PRIVATE PRACTICE	
	CASES NUMBER	IMPROVED PER CENT	CASES NUMBER	IMPROVED PER CENT
Pyribenzamine only	21	48	5	20
Preseasonal injections plus usual drugs	18	56		
Coseasonal injections plus usual drugs			4	50

B. Ragweed Bronchial Asthma.—(Table II) Twenty-one patients with bronchial asthma due to ragweed pollen were treated with pyribenzamine alone. Forty-eight per cent of this group were improved. Of 18 patients treated by pollen injections, ephedrine, etc., 56 per cent were benefited. Of the group in private practice only one of the five patients treated with pyribenzamine alone had satisfactory relief of symptoms, while two of four patients given coseasonal therapy plus ephedrine, aminophyllin, etc., were improved.

TABLE III. SUMMARY OF RAGWEED STUDIES

TREATMENT	HAY FEVER		ASTHMA	
	CASES NUMBER	IMPROVED PER CENT	CASES NUMBER	IMPROVED PER CENT
Preseasonal injections plus usual drugs	27	67	18	56
Pyribenzamine only	54	72	26	41
Coseasonal injections plus usual drugs	10	60	4	50

Table III illustrates in summary the comparative results of the two methods of treatment in hay fever and asthma. As may be seen from this table, 72 per cent of 54 patients with ragweed hay fever treated with pyribenzamine alone had relief of symptoms. Sixty-seven per cent of 27 hay fever patients given adequate specific hyposensitization therapy plus the usual drugs were benefited. Coseasonal intradermal injection therapy plus the usual drugs gave relief in 60 per cent of ten patients. In bronchial asthma due to ragweed pollen, pyribenzamine gave relief in 41 per cent of the patients so treated, whereas, 56 per cent improved on pollen treatment and 50 per cent on the coseasonal therapy.

EVALUATION OF RESULTS BY PUNCH CARD DATA

In order to check on the results obtained from the review of the outpatient charts and symptom cards, another method of evaluating the results of therapy was obtained by data from a special punch card supplied by the International Business Machine Company (Chart 1).

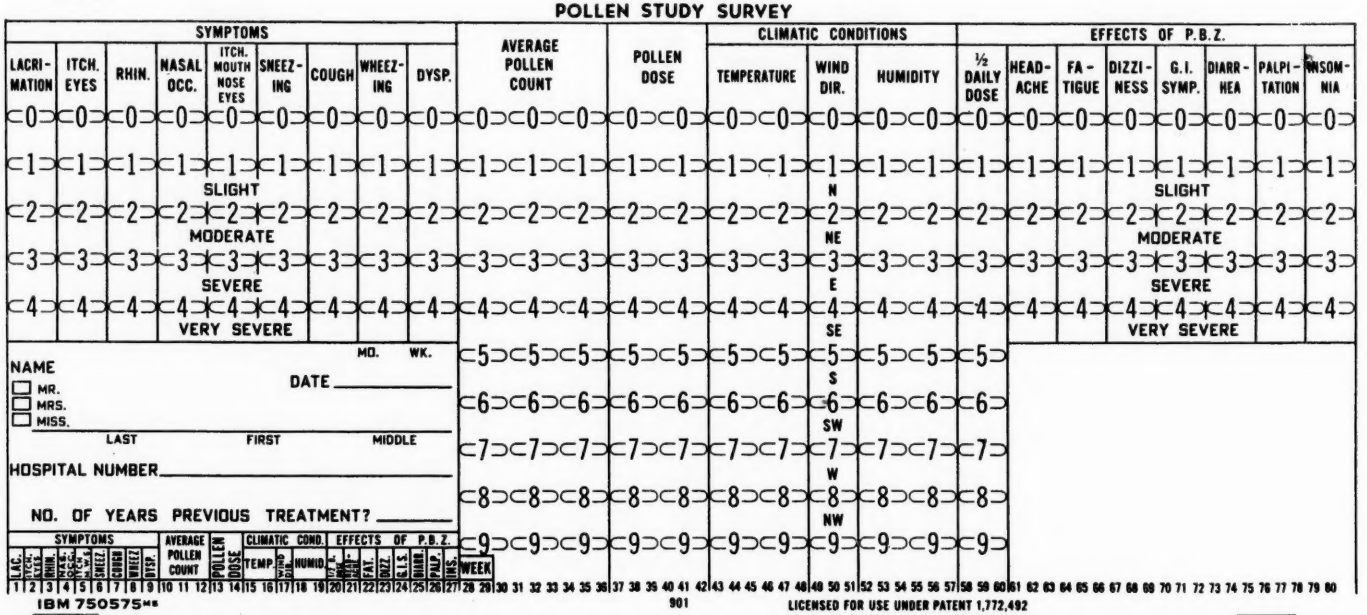
At each visit the patient was carefully questioned about the occurrence of each symptom during the preceding twenty-four hours and the severity from 0 to 4 was graded on this card with a graphite pencil. If the patient belonged to the group receiving pollen injections the dosage was recorded, and if pyribenzamine was used, the dosage and side-effects as to severity (0 to 4) was likewise noted. Other data such as pollen counts, temperature, humidity, and wind direction were also marked on the cards. At the end of the ragweed pollen season these cards were then sent to the International Business Machine Company where various correlations and results were tabulated. From these data the following graphs were prepared.

A. Symptoms.—The intensity of total hay fever symptoms present is shown on Graph 1. No significant difference in the various types of therapy could be determined.

Graph 2 shows each of the individual symptoms and the relative intensity under the various methods of treatment. The results are essentially the same in the pyribenzamine and the injection groups.

Graph 3 illustrates the summation of all asthmatic symptoms due to ragweed pollen as treated in the three groups. Little difference was noted among the three groups.

Graph 4 shows a breakdown of the individual symptoms of asthma. It appears that the preseasonal and coseasonal injection treatments are superior to the use of pyribenzamine alone in relieving asthma.


POLLEN STUDY SURVEY
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LACRIMATION
ITCH. EYES
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NASAL OCC.
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AVERAGE POLLEN COUNT
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CLIMATIC CONDITIONS
TEMPERATURE
WIND DIR.
HUMIDITY
EFFECTS OF P.B.Z.
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HEADACHE
FATIGUE
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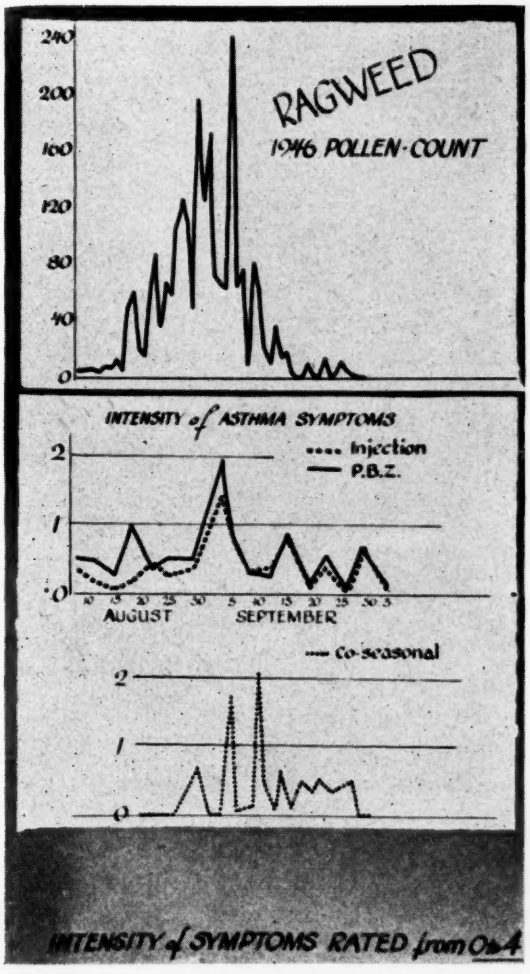
Chart 1.

These same punch cards enabled us to obtain data on several other variable factors related to this study.

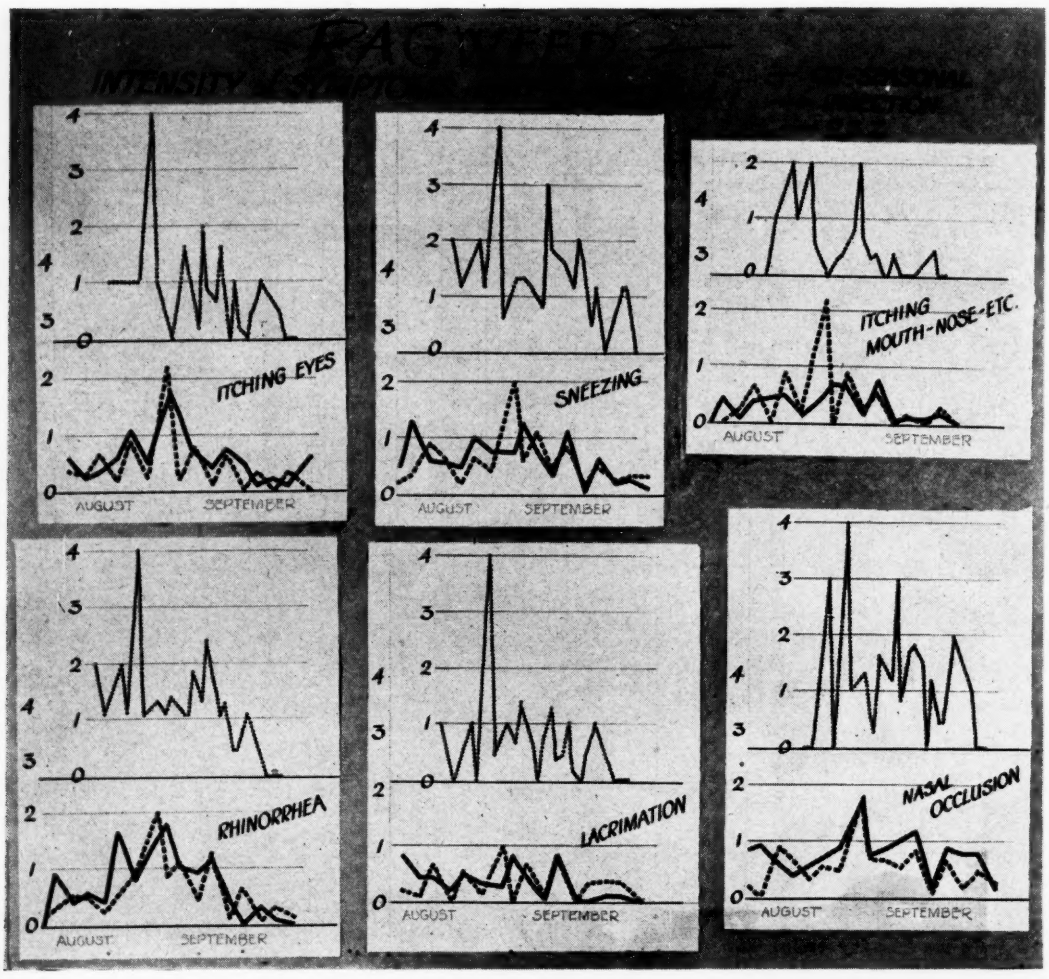
B. Pollen Dosage.—All patients in the group treated with pollen extracts received adequate dosage. However, the maximum dose varied with the degree of sensitivity of the patient. There was no apparent correlation between the amount of pollen extract given and the severity of either the hay fever or asthma symptoms during the season (Graph 5). Apparently each patient had received the dose he could tolerate and had derived the maximum benefit therefrom.



Graph 1.

C. Pyribenzamine Dosage.—The dosage varied with each patient, and also in the same patient dependent upon the symptoms present. Fifty milligram tablets were prescribed at first to be taken two to four times daily. If this amount was not sufficient to control symptoms, the dosage was gradually raised.

It will be noted that, if patients did not obtain relief with 100 mg. four times daily, the ingestion of more pyribenzamine did not improve their symptoms (Graph 6).



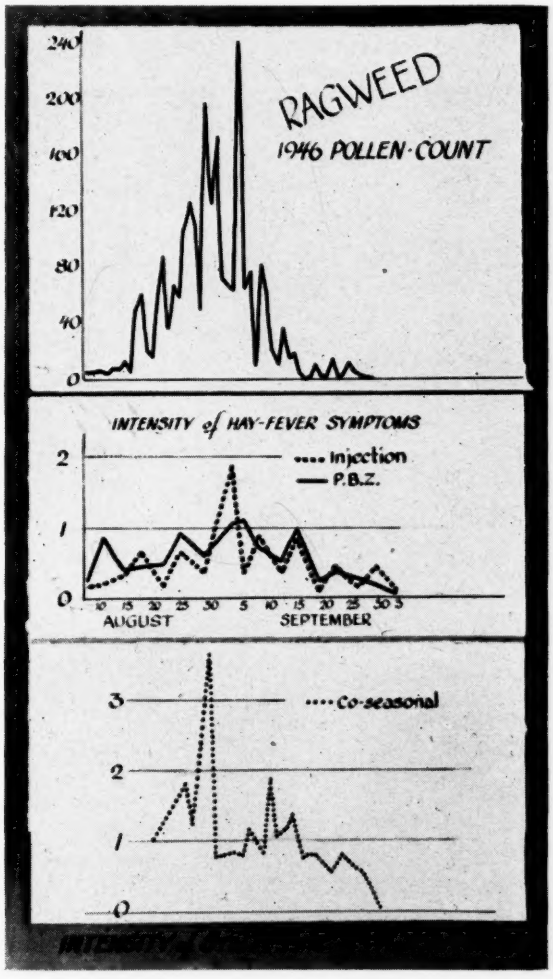
Graph 2.

D. Side-Effects of Pyribenzamine.—The list of side-effects of pyribenzamine and their incidence are shown in Table IV. The most common side reaction was fatigue which was present to some degree in 18 per cent of the patients. However, it was moderate to severe in intensity in only 8 per cent of the patients. From the study with these cards the previous observations were confirmed, i.e., the incidence of side reactions definitely increased with administration of large amounts of the drug. (Table V)

E. Miscellaneous Findings.—No relationship of intensity of symptoms of either hay fever or asthma to temperature or humidity was noted. It has often

TABLE IV. PYRIBENZAMINE INCIDENCE OF SIDE-EFFECTS

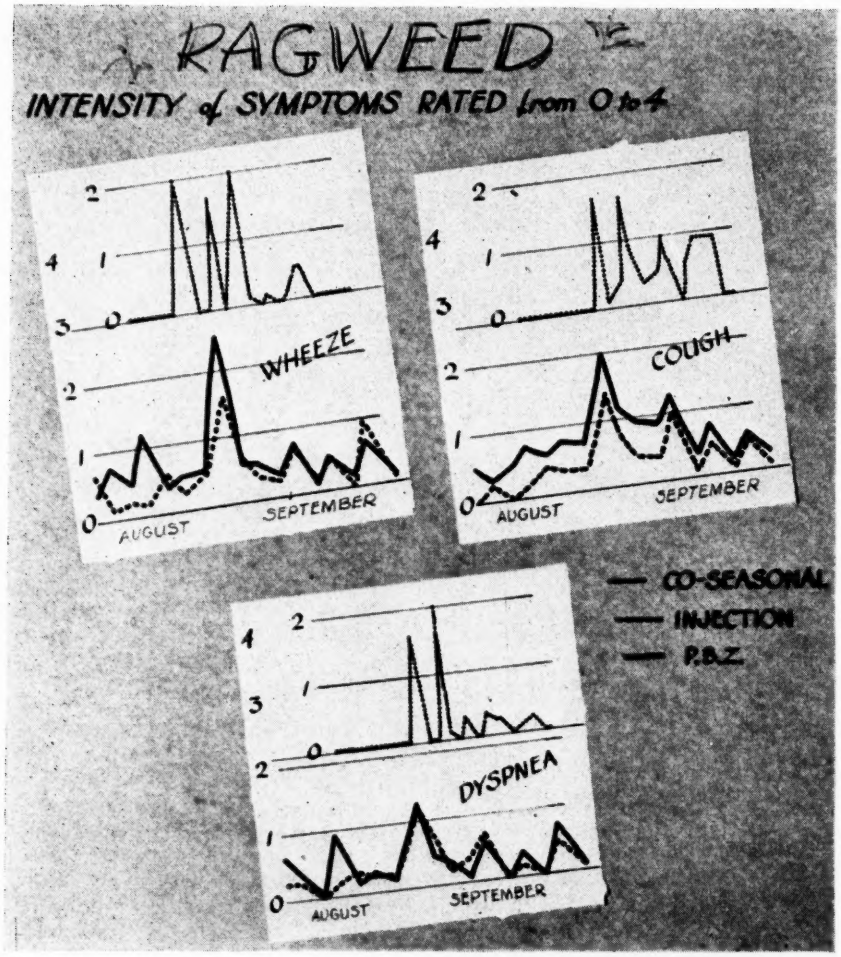
	TOTAL (PER CENT)	MODERATE, SEVERE OR VERY SEVERE (PER CENT)
1. Fatigue	18	8
2. Headache	13	3
3. Dizziness	8	3
4. G-I symptoms	8	2
5. Insomnia	5	1
6. Diarrhea	3	1
7. Palpitation	3	1



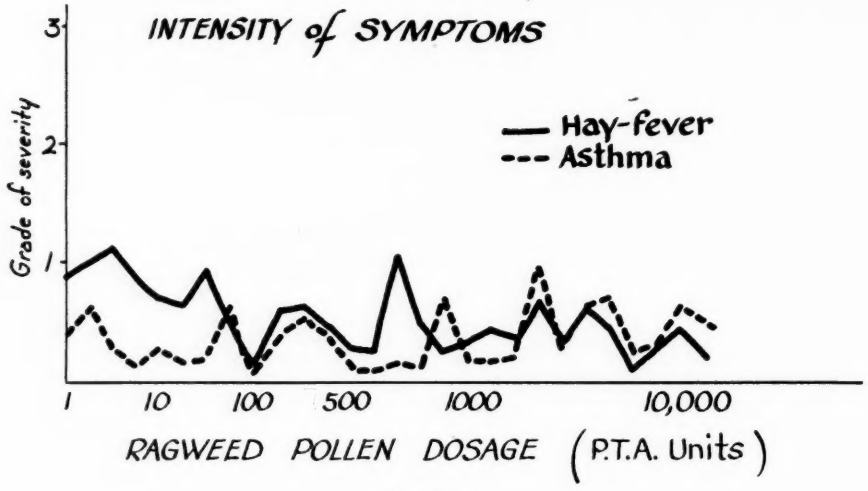
Graph 3.

been stated that asthma is worse when the humidity is high. This was not borne out in the analysis of the punch cards.

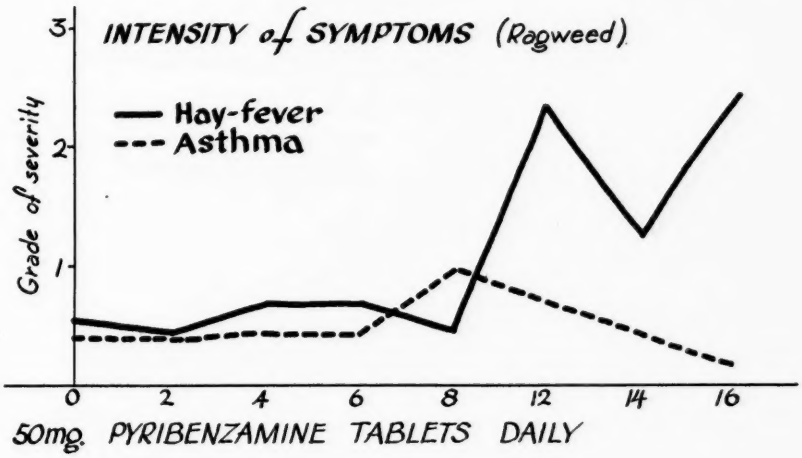
Likewise, there was no correlation between the ragweed pollen count and the temperature or humidity. However, there was an apparent relationship



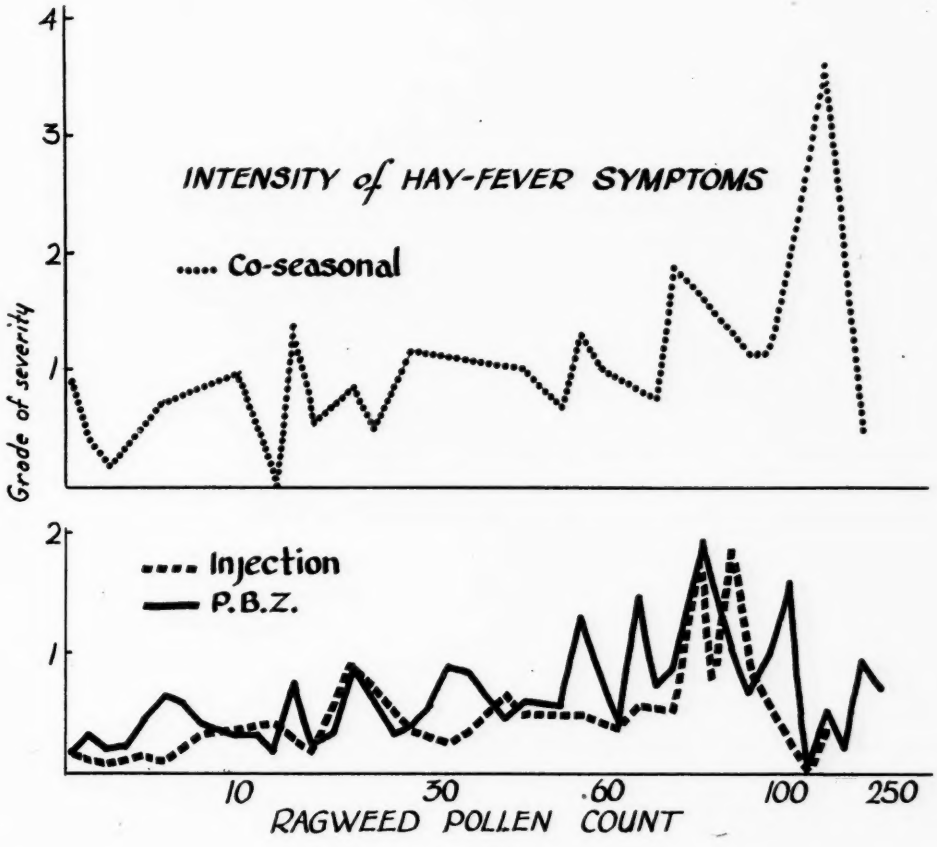
Graph 4.



Graph 5.



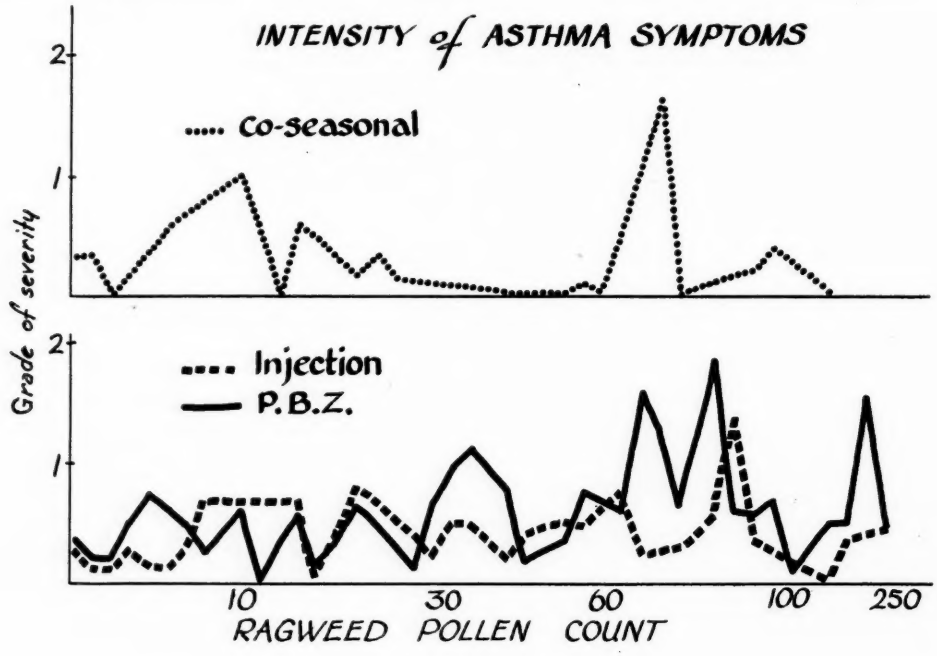
Graph 6.



Graph 7.

TABLE V. RELATIONSHIP OF PYRIBENZAMINE DOSAGE TO SIDE-EFFECTS

DAILY DOSE OF PYRIBENZAMINE MG.	100	200	300	400	600	700	800
1. Fatigue	6	6.7	14.0	13.0	25.0	--	--
2. Headache	5	4	4.7	6.0	--	25.0	--
3. Dizziness	1.6	3.0	3.9	4.5	--	--	--
4. G-I symptoms	2.7	2.6	0.8	3.5	--	--	--
5. Insomnia	1.3	2.6	2.4	1.5	--	--	--
6. Diarrhea	1.6	0.7	0.8	2.0	--	--	--
7. Palpitation	1.0	1.5	2.4	0.5	--	--	--



Graph 8.

of intensity of symptoms of hay fever or asthma to the pollen counts in the three groups. (Graphs 7 and 8)

It is interesting to note, however, that the pollen counts were highest in Buffalo when there was a prevailing west wind. The greatest intensity of symptoms in ragweed hay fever was noted with this wind direction. The next highest pollen counts were found with a prevailing northeast wind, as were the next most intense hay fever symptoms.

OBSERVATIONS ON PRIVATE PATIENTS

Another phase of the study was performed in private practice. These data were obtained only from the charts and the patients answering questionnaires sent to them at the end of the pollen season. In this study all patients had had adequate perennial or preseasonal pollen injections. There was a total of 242 patients (Table VI). Of this group, 106 received excellent relief without requiring *any* additional palliative measures. One hundred thirty-six patients were not receiving satisfactory relief as the pollen season advanced and, hence,

TABLE VI. RAGWEED STUDIES IN PRIVATE PRACTICE

	NO. OF CASES	IMPROVED	LESS THAN 50% IMPROVEMENT	PER CENT IMPROVED 50%
Adequate hyposensitization	242	106	136	44

EFFECT OF ADDING PYRIBENZAMINE TO 136 CASES OF RAGWEED POLLINOSIS IN WHICH THERE WAS UNSATISFACTORY RESPONSE FROM ADEQUATE HYPOSENSITIZATION ALONE

	NUMBER OF CASES	IMPROVED	PER CENT IMPROVED
Hay Fever symptoms	134	123	91
Bronchial symptoms	39	24	61

were given pyribenzamine in addition to their injection treatment. Of this latter group, 134 patients had nasal symptoms, of whom 123 (91 per cent) obtained relief with the combined treatment of injection and pyribenzamine. Thirty-nine patients had bronchial symptoms, and 24 (61 per cent) were benefited.

The combination of adequate preseasonal injections plus pyribenzamine in palliative amounts as needed gave satisfactory relief in 95 per cent or 242 patients with hay fever in private practice.

DISCUSSION

Treatment of ragweed hay fever with pyribenzamine alone was, in our study, as effective as the usual injection treatment in the relief of symptoms in clinic patients. On the other hand, injection therapy plus the usual symptomatic drugs such as iodides, ephedrine, and aminophyllin were superior in alleviating bronchial symptoms than was pyribenzamine alone.

From our clinical experience in the past, and the results presented here, there can be no question but that the antihistaminic drugs, of which pyribenzamine is one, are of value in the treatment of ragweed hay fever. Pyribenzamine alone, in sufficient dosage, may control the symptoms of seasonal allergic rhinitis to a great degree, but cannot give as adequate relief as does adequate hyposensitization treatment plus pyribenzamine. The incidence of side-effects from this drug are small when given with the specific hyposensitization therapy because smaller doses are required to control the symptoms.

SUMMARY

1. Pyribenzamine plus adequate injection therapy gave relief of symptoms in 95 per cent of 242 private patients suffering from ragweed hay fever.

2. In clinic patients, pyribenzamine alone relieved hay fever symptoms to about the same degree as did the specific hyposensitization therapy plus symptomatic drugs.

3. Increased humidity was not related to an increase in seasonal asthmatic symptoms.

4. There was no consistent correlation between temperature, pollen counts, and pollen dosage to the intensity of symptoms.

5. The IBM punch cards are an excellent means of studying variables in a survey such as this.

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DISCUSSION

DR. ROBERT CHOBOT (New York).—Dr. Arbesman and his associates are to be congratulated for a very interesting study on one of the most important problems facing us today, namely, the type of therapy for the pollen-sensitive patient. I do not find that his figures differ so very markedly from my own experience, but I should like to discuss them in a little more detail.

In his group of patients treated with pyribenzamine alone, his figures are definitely higher than those of most of the members of the Committee of Therapy. Our average figure of improvement on pyribenzamine alone, with no other type of therapy, is about 50 per cent in a series of 100 cases. His figure of 72 per cent improvement in a series of 54 cases is definitely higher.

He believes, and I concur, that hay fever symptoms on pyribenzamine are definitely less where combined with pollen injections than with the use of the drug alone. I cannot help but feel that his figure of 91 per cent relief of symptoms in the hay fever cases treated in his office with ragweed and pyribenzamine is certainly higher than those reported by anyone else.

Our opinion is that the figure varying anywhere from 60 to 70 per cent, which he found in his clinic patients so treated, was more nearly the accurate figure, and in over 1,000 cases of hay fever treated with ragweed injections and pyribenzamine which the Committee of Therapy has accumulated, 63 per cent was the average figure we arrived at.

When it comes to the consideration of asthma—pollen asthma—I again find myself in accord, as our experience on the Committee has shown, that pyribenzamine is least efficacious in controlling asthmatic symptoms generally, particularly where there is an infectious element present.

There is no question that the use of antihistaminic drugs, pyribenzamine particularly, in the treatment of hay fever symptoms is of great value and represents an enormously

important contribution to the pharmacology of allergy; however, the important thing to remember in any of these statistical studies is that it is very difficult for the physician and even the patient to be entirely objective. This is a great weakness, and one which has been apparent to me in the compilation of our figures on the Committee. It is impossible for a physician, being only human, not to be prejudiced either for or against a drug. This was apparent in the range of figures submitted by various observers in different parts of the country.

They varied anywhere from 16 per cent to 88 per cent benefit in the treated cases. Likewise, the technique by which these statistical studies and figures is arrived at is important. It is possible to get a figure of 72 per cent complete relief with pyribenzamine alone, if you calculate your figures on symptom-free days, taking a 42-day period and removing the free days. We must remember that there are many free days in the season. The same group evaluated on an average impression of the patient drops very precipitously from 72 per cent down to about 50 or 45 per cent.

I am of the firm conviction that the only way a therapeutic trial can be made to eradicate the personal element is to have matters so arranged that the doctor himself does not know whether he is treating his patients with placebos or whether he is treating them with the medication. It is only by using this type of blindfold test that I think the element of overenthusiasm can be removed.

As far as the dosage of pyribenzamine is concerned in the treatment of these cases, my experience is that if pyribenzamine does not help the patient, increasing the dose beyond a reasonable degree is likely to be rather ineffective. This is also Dr. Arbesman's experience. Also, I feel that as the patients continue to take the medication, there is a definite development of tolerance and a loss of efficiency of the drug. I do not believe that this phase of the therapy has been sufficiently stressed, and if this should be true, it certainly would be another weakness, but not an unexpected one.

Dr. Arbesman's observation that the IBM cards contradicted the other clinical charts —he found, as I understood it, in his paper, that when he went over the clinical charts he arrived at one figure, and when he had the results tabulated on his IBM cards and put through a statistical machine, the figure was appreciably lower—that fact alone indicates the care that must be used in any statistical evaluation.

I find myself in complete accord with Dr. Arbesman and his co-workers in their interpretation of the value of this study, but may I point out that, after all, any statistical study will not have the last say in the decision as to what treatment is to be and whether treatment is to follow the lines of our own personal recommendations. There is no question that such a study as this, or the report which the Committee on therapy will present tomorrow are of great help, but the answer as to whether antihistaminic drugs are going to be effective in the treatment of hay fever, alone, is going to be decided by two elements. In the first place, it will be decided by the severity of the grass and ragweed seasons in the next few years. Remember that the 1946 hay fever season was about the lightest we have ever had. Second, it is going to be decided by a large number of patients who are going to undergo self-medicated therapy. If they are successful, the use of antihistaminic drugs will become in time the method of election.

On the evidence presented by this paper, and on my own personal experience, I do not feel that there is very much danger of that happening. Certainly those patients who have any tendency toward asthma are going to be in serious trouble. The remaining patients who have simple, uncomplicated hay fever have been benefited in a very light ragweed year; therefore, the expectation is fairly sound that when the hay fever season with a heavier degree of pollenation occurs, many of these will not remain symptom-free.

DR. ARBESMAN (Closing).—I wish to thank all the discussers for their interesting remarks. There are enthusiasts and hyperenthusiasts, I guess, about any method of therapy. Probably I am one of the enthusiasts.

In answer to the question of effect of this drug on the blood, we have been working with these drugs now for well over two years and have done blood studies, including complete blood counts, on patients who have been on this drug. No abnormal changes were noted.

Many patients have been on this drug for over two years and have not developed any tolerance as yet. The ragweed pollen count in Buffalo this year was perhaps two-thirds that of 1945. However, our results in private practice cases in our study in 1945 were essentially the same as with the private cases we presented here.

The reason for the discrepancy in results between private patients and clinic patients may be explained by the fact that the private patients are more adequately supervised. They are seen every other day, and the pyribenzamine dosage is more frequently adjusted. Perhaps, too, they are milder cases than the clinic patients who come in only if they have very severe symptoms.

We tried to be unbiased in our analysis of these results. We had one person, who did not know what the patient was getting, record the intensity of symptoms on these IBM cards.

The results from Postgraduate Hospital Allergy Clinic are, indeed, very interesting. No matter how you evaluate symptoms and results of therapy with hay fever, whether you call it hours of improvement, hours of trouble, or slight, or severe symptoms, it still is a subjective analysis, and it is very difficult to evaluate completely.

From the charts we had there, we could divide our patients into a number who had very severe symptoms, the number who had moderate symptoms, and those who had slight symptoms, and no symptoms at all. I did not bother to go into all that for you, but here again the results of the two methods of treatment seem to be approximately the same.

The question is, is it worth while for the patient to take injection therapy, or should he just try pyribenzamine alone? That is a problem that is going to await further study. I cannot answer that at this time, despite the fact that we have used the drug now for well over two years.

PENICILLIN AEROSOL IN THE PREVENTION AND TREATMENT OF RESPIRATORY INFECTIONS IN ALLERGIC PATIENTS*†‡

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INFECTION plays a major role in the production of allergic symptoms in the respiratory tract.[1] It may initiate asthma without any other evidence of hypersensitivity (infective asthma) or it may engraft itself upon a previously existing allergic state and, in turn, participate as a specific factor (mixed asthma). According to Burky,[2] toxins produced by infection may induce autosensitivity wherein hypersensitivity is acquired by the organism to its own tissues.

Chronic sinusitis, bronchitis, and bronchiectasis are, therefore, frequent complications found by the allergist. His approach must, consequently, be twofold—to discover the underlying allergy, if present, and to eradicate any superimposed infection in the respiratory tract. We believe the most common cause of status asthmaticus to be infection.

Penicillin has been used by injection, by inhalation, and orally for the treatment of asthma associated with infection. Analyses of the reports by Derbes,[3] Leopold and Cooke,[4] and by Leopold[5] indicate that penicillin administered parenterally has proved of little avail in the treatment of asthma, except in few isolated instances. Hampton and his associates[6] tried both intramuscular injections and intratracheal spray, respectively (with penicillin), with poor results. Barach and associates,[7] employing methods initiated by Abramson,[8] and developed by Bryson, Sansome, and Laskin,[9] treated asthma and respiratory infections with penicillin aerosol, and reported some degree of success. With an additional mechanism employing intermittent suction, Barach[10] has also treated infection in the sinuses. Vermilye[11] reported the treatment with penicillin aerosol of 25 patients suffering from asthma, with good results in all. This was commented upon by Engelsher[12] in a letter to the Editor of the *Journal of the American Medical Association*, in which he reported that only 15 per cent of 74 patients showed some improvement from penicillin aerosol therapy. Likewise, he reported poor results with penicillin given orally or parenterally. Recently, Baumann and her associates[13] reported that penicillin administered orally was of value in the treatment of asthma.

It is pertinent to mention the experimental studies of Kreuger and his co-workers,[14] who showed that an inhaled aerosol is widely distributed throughout the lung fields. The efficiency of penicillin aerosol was investigated by Wilson and her associates[15] who treated experimental pneumonia with this, and

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showed it to be as effective as when introduced parenterally, and under certain conditions more effective.

This report is based on the treatment with penicillin aerosol of 111 patients, of whom 88 displayed respiratory allergy in addition to infection (Table I). Sixty-one suffered from asthma. Twenty-seven presented evidence of upper respiratory infection (acute or chonic) together with nasal allergy. The remaining 23 patients were treated for respiratory infection not associated with allergy, and are not analyzed at this time.

TABLE I. CLASSIFICATION OF PATIENTS TREATED WITH PENICILLIN AEROSOL

1. Asthma associated with infection	61
2. Acute upper respiratory infection	14
3. Chronic upper respiratory infection	13
4. Bronchiectasis, bronchitis, etc.	23
Total	111

PRODUCTION OF PENICILLIN AEROSOL AND METHODS OF UTILIZATION

Aerosolization was effected by means of a combined steam generator and aerosolizer previously described.[16, 17] It has some advantages over the conventional oxygen nebulizer method. It is more economical to operate, and its small size makes it convenient for use at home, in the office, or in the hospital. The apparatus is capable of aerosolizing large quantities; combined aerosols are, therefore, practical. It produces a warm, moist aerosol capable of giving high therapeutic blood levels of penicillin.[18] Self-treatment by the patient is readily learned, particularly for the administration of aminophyllin aerosol.

By means of this apparatus aerosols for experimental or therapeutic purposes have been produced with epinephrin, neosynephrin, aminophyllin, ammonium chloride, benadryl, propylene glycol, penicillin, sodium sulfadiazine, sodium sulfacetemide, and insulin. Combined aerosols containing two or more of these have been employed as well.

Some patients were treated by simple open inhalation, by breathing penicillin* aerosol as it was produced. This was wasteful of penicillin because of rapid dissipation, since this was an aqueous aerosol and was relatively unstable. To stabilize the aerosol, penicillin was dissolved in 20 c.c. of propylene glycol to which was added 2 c.c. of glycerine. Conservation of this aerosol was obtained by confining it in a limited space—a small chamber, a tent, or a breathing box. Penicillin blood level studies[18] of patients with *normal lungs* had revealed that particularly effective therapeutic blood levels of 6-hour duration could be obtained with the tent or breathing box methods (Table II). The latter is a simple container (box) into which the penicillin-propylene glycol aerosol mixed with steam is blown. The patient inhales from this box by means of an oronasal mask connected by tubing to the container confining the aerosol. Flutter valves are so placed that the patient inhales from, but cannot exhale into the box, preventing the accumulation of carbon dioxide. Exhalation is effected through a nasal flutter valve, permitting no inhalation through this aperture (Fig. 1).

*Ca penicillin was used in these studies, and was provided through the courtesy of Schenley Laboratories, Inc., New York City.

TABLE II. REPRESENTATIVE PENICILLIN BLOOD LEVELS IN PATIENTS WITH NORMAL LUNGS, OBTAINED BY VARIOUS METHODS OF AEROSOL THERAPY

METHOD OF ADMINISTRATION	UNITS OF PENICILLIN	DILUENT	UNITS OF PENICILLIN/CC OF SERUM HOURS						
			1/2	1	2	3	4	5	6
Airtight Chamber 6 feet × 6 feet × 7 feet	180,000	Propylene glycol	1.0	0	0	0	0	0	0
Open Inhalation	50,000	H_2O	.4	0	0	0	0	0	0
	100,000	H_2O	1.2	1.0	.6	0	0	0	
Tent Method	100,000	H_2O	.6	0	0	0	0	0	0
(in tent for 1 hr.)	100,000	Propylene glycol	.25	.25	.25	.25	.125	.125	–
Breathing Box	50,000	Propylene glycol	1.0	1.0	1.0	1.0	1.0	1.0	0.5

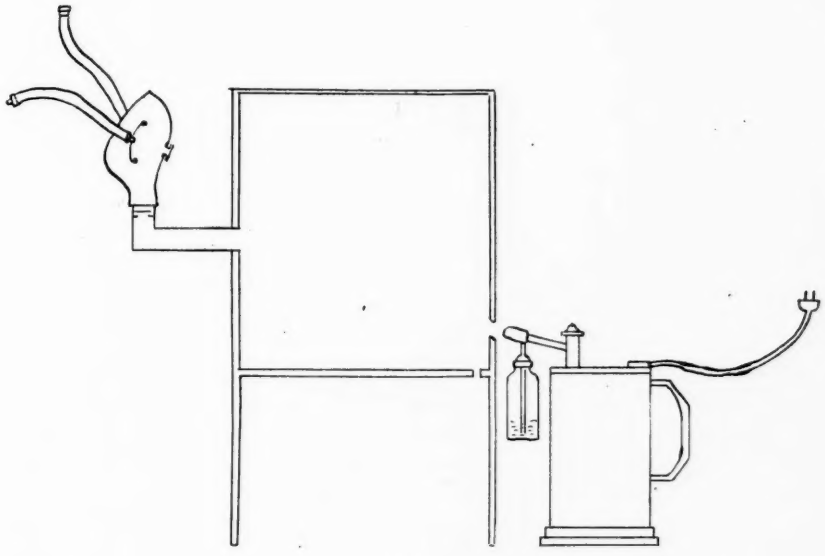

Fig. 1.

The breathing box makes penicillin aerosol therapy a simple office procedure, and most of the patients reported here were treated in this fashion.

In view of the penicillin blood level studies recorded in Table II, a minimum dose of 100,000 units per day for five days was decided upon. By open inhalation 30 to 50,000 units three to four times a day were administered. Propylene glycol was used as the solvent where the patient was treated either in the chamber, under the tent, or with the breathing box. The glycol with the addition of glycerine produced a long-lasting aerosol. For the tent, 100,000 units were administered twice daily; for the chamber the dosage was 200,000 units twice a day; with the breathing box 100,000 units were administered daily, or 50,000 units twice daily. The total dosage administered in a course of treatment varied from 500,000 to 1,500,000 units.

The mild ambulatory cases were subjected to single daily treatments. Severer asthma required more frequent treatment, preceded at times by aminophyllin and/or ammonium chloride in aerosol form. The aminiphyllin aerosol

dosage varied from 0.25 Gm. to 0.5 Gm. in 10 or 20 c.c. of water. Where the sputum was thick and gelatinous, ammonium chloride (10 c.c. of a 5 per cent solution) was used in combination with aminophyllin, prior to penicillin therapy, in order to increase the vital capacity, thereby making penicillin aerosol more effective.

Where sodium sulfadiazine in aerosol form was used following penicillin aerosol therapy, a 5 per cent solution was employed, giving 20 to 30 c.c in several daily treatments.

For *prophylactic purposes*, when indicated, a daily dose of 100,000 units of penicillin in propylene glycol was administered for three days, through the breathing box.

Penicillin aerosol therapy is of value only where there is definite evidence of infection in the respiratory tract. A history of asthma following a true cold, and asthma associated with sinusitis, bronchitis, or bronchiectasis are indications for penicillin therapy. Fever, leucocytosis, elevated sedimentation rate, and x-ray evidence of infection in the sinuses or chest also indicate the need for antibiotic therapy. In short, one treats the infection present and not the asthma per se.

RESULTS OF TREATMENT OF ASTHMA WITH PENICILLIN AEROSOL

In Table III are summarized the results of treatment of 49 patients with asthma and associated infection. Forty of these were treated with the *breathing box*. These patients were grouped according to the severity of the asthma. Group I—mild periodic asthma responsive to simple oral medication; Group II—moderate asthma, usually daily, and responsive to oral or rectal medication, or epinephrin by inhalation; Group III—severe asthma occurring daily and requiring parenteral injections of epinephrin or aminophyllin for relief. Group IV—severe continuous asthma, unresponsive to the usual therapy—*status asthmaticus*—was treated by open inhalation described below. Such a classification was necessary to evaluate properly the therapy employed.

Thus, when patients with mild asthma (Group I), which usually followed a cold and had a tendency to persist, were treated with penicillin aerosol, there was an effective immediate response in all cases. Asthmatic symptoms disappeared from one to several days following the institution of treatment. Cessation of coughing was one of the early signs of improvement.

In view of the mildness of these cases of asthma, it is conceivable that some patients would have recovered spontaneously; nevertheless, the close association between treatment and relief of symptoms was such as to warrant the impression that a steam-generated aerosol of penicillin in propylene glycol was markedly effective in the treatment of these mild cases of infective asthma. Corroborative evidence of the efficiency of penicillin in these cases was also seen in the elimination of purulent nasal or bronchial secretions. With few exceptions, where the purulent secretions disappeared, there was concurrent relief of asthmatic symptoms.

Grade II asthma was less responsive to treatment (80.9 per cent immediate improvement), and Grade III much less (40.0 per cent as recorded in Table III. It was noted that even when there was a favorable response to treatment, it was frequently of short duration. Table III, therefore, records the condition of the patient one month following treatment.

The causes for failures and relapses will be considered later.

TABLE III. RESULTS OF TREATMENT OF ASTHMA WITH PENICILLIN-PROPYLENE GLYCOL AEROSOL, UTILIZING THE BREATHING BOX, TENT AND CHAMBER METHODS

METHOD OF TREATMENT	DOSE OF PENICILLIN IN PROPYLENE GLYCOL	GRADE OF ASTHMA*	NO. OF PATIENTS TREATED	IMPROVEMENT			
				IMMEDIATE		1 MONTH LATER	
				NUMBER	PER CENT	NUMBER	PER CENT
Breathing box	100,000 units daily or 50,000 units twice daily	Grade I	9	9	100	7	77
		Grade II	21	17	80.9	13	61.9
		Grade III	10	4	40.0	4	40
Tent Method	100,000 units twice daily	Grade III	6	4	66.6	3	50
Chamber Method	200,000 units twice daily	Grade II	3	2	66.6	1	33.3
		Total	49	36	73.7	28	57.1

*Grade I—mild; Grade II—moderate; Grade III—severe; Grade IV—*status asthmaticus.*

The *tent method* of treatment with penicillin-propylene glycol aerosol was used in only six cases. Originally designed for children, the tent was constructed of completely transparent material; nevertheless, some children could not be confined in this tent because of apprehension and heat. The temperature within rises to about 90° F., with a humidity of about 90 per cent. One adult was definitely worse as a result of the humidity. Although she could not tolerate the tent treatment, she did respond to open inhalation.

To relieve the discomfort due to heat and humidity, only the head is now kept under the tent, and the rest of the body is exposed as much as possible to increase heat radiation. This has proved more tolerable. Confinement under the tent for one hour is desirable, although the actual period of aerosolization may last only about fifteen minutes. Relatively severe cases (Grade III) were treated in this fashion, and four of the six patients responded favorably. Aminophyllin aerosol was given by open inhalation prior to this treatment, if the dyspnea were severe.

The *chamber method* had given such poor blood levels in the original studies that we did not make much use of this procedure. The first patient, an adult, was treated with 180,000 units in propylene glycol, and was confined for three hours in a chamber 6 feet by 6 feet by 7 feet. Following this one treatment, he was free from asthma for three months. Subsequent penicillin aerosol treatment, similarly administered, did not give the same results.

This procedure was modified for the home treatment of two asthmatic children. The bathroom was utilized as the aerosolizing chamber. To maintain the aerosol, the room was first warmed by filling the bathtub full of hot water. Then the penicillin in propylene glycol was aerosolized slowly, with the patient sitting close to the aerosolizer. The aerosol was maintained in this fashion for one hour

(the duration of a treatment). The room temperature varied, in one series of observations, from 72° to 92° F. with the humidity ranging from 70 to 88 per cent. This procedure has proved tolerable to the younger patient. Apprehension was reduced by the fact that the bathroom is a familiar one and is associated with the pleasure of bathing, as well as by the presence of one of the parents, who can play with the child while undergoing treatment. It is advisable that if one of the parents shows evidence of respiratory infection, that that parent administer the treatment; thus, two patients are treated at the same time and a possible carrier may be eliminated, because reinfection seems to occur so often in these children.

Very satisfactory results were obtained with one child, while another one had only temporary relief following the treatment. The dose, because of the size of the room, must necessarily be higher; in addition, two people are inhaling the aerosol. These children were, therefore, treated with doses of 200,000 units twice daily, for five days. This is a relatively simple home treatment, and further studies are needed to determine its true value.

Of the 49 patients treated with penicillin-propylene glycol by the various methods, as recorded in Table III, 2 were given 1,500,000 units in one course of treatment, 16 had 1,000,000 units, while 31 patients had a total dosage of 500,000 units. Thirty-three patients were given single daily treatments; the remainder (16) were given two or more treatments per day.

In view of recurrences, several patients were given more than one course of treatment. Within one year's time 41 patients had one course of treatment; five were treated twice; two were treated three times, and one was given four courses of treatment including one for prophylactic purposes.

The *open inhalation method* was used primarily in the treatment of the hospitalized cases of *status asthmaticus* (Grade IV asthma). These patients resist confinement of any kind, including the oronasal mask. Furthermore, it was considered advisable to give preliminary aerosols of aminophyllin alone, or in combination with ammonium chloride. The aminophyllin increased the vital capacity, thereby permitting greater utilization of the penicillin aerosol which followed. A reduced vital capacity markedly limits the amount of penicillin aerosol entering and being absorbed from the respiratory tract (Chart I). The ammonium chloride in aerosol form helped to liquefy the thick tenacious sputum and increased expectoration, thereby adding to the improvement of the vital capacity. Three patients in *status asthmaticus*, treated with preliminary aminophyllin aerosol followed by penicillin aerosol, responded well, although one of these had a return of symptoms in moderate form within a month.

Nine hospitalized patients suffering from *status asthmaticus* were treated with a combination of aminophyllin and ammonium chloride in aerosol form. This was followed by a course of penicillin aerosol, and in turn followed by sodium sulfadiazine aerosol two to four times daily. The sulfadiazine was added because the bacteriologic investigation of the sputum had shown a mixed flora in which not all of the organisms were presumably responsive to penicillin. This was confirmed clinically when the sputum failed to clear after adequate penicillin therapy, and did clear after sulfadiazine therapy. The combination of these

aerosols was effective in the treatment of 8 (88.8 per cent) of these difficult cases. This is a rational and effective treatment, although apparently temporary in nature, since four of those who responded had a return of their symptoms at times in a milder form within a month.

RESULTS OF TREATMENT OF UPPER RESPIRATORY INFECTION ASSOCIATED WITH NASAL ALLERGY

Twenty-eight patients with upper respiratory infection superimposed on an underlying allergy were treated with the breathing box, inhaling penicillin-propylene glycol aerosol, 100,000 units daily, usually for five days, occasionally longer.

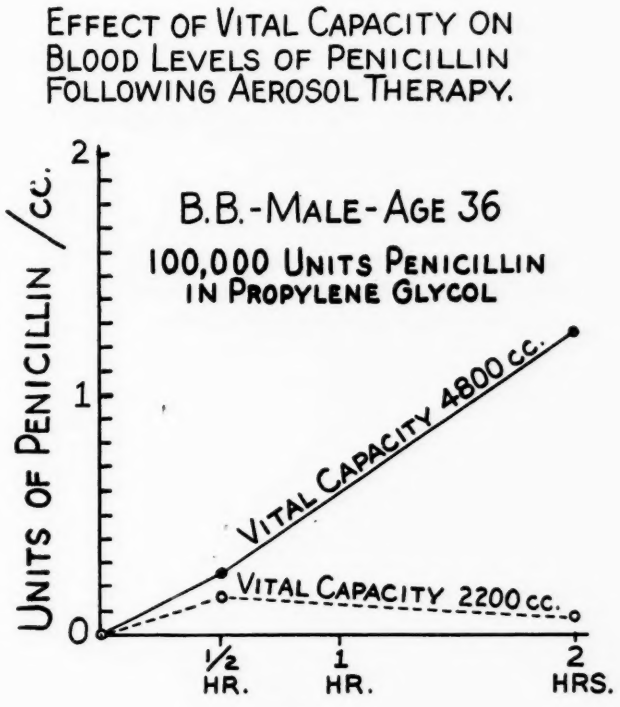

Chart 1.

In analyzing the results of the group of cases herein considered, it was thought advisable to separate them into two groups—acute and chronic. Some of these cases presented clinical and x-ray evidence of sinusitis. These included asthmatic patients who, under the usual antiallergic treatment, had their asthma under control but the nasal difficulties continued—clogging of the nose, purulent nasal discharge, postnasal drip, particularly on arising, sometimes inducing vomiting and coughing. Although these patients did not respond to allergic treatment, 11 of 13 (84.6 per cent) in the chronic category did respond to penicillin aerosol.

The acute cases responded almost as well, although it was difficult to evaluate results here since the acute upper respiratory infection, in most instances, is

a self-limiting disease. One cannot measure the role of natural immunity in these cases. Those with primary nasal allergies (hay fever or perennial allergic rhinitis) gave histories of "colds" of long duration. With penicillin aerosol therapy the duration of the "colds" was definitely reduced.

Of the 14 patients with acute upper respiratory infections, 11 (78.8 per cent) reported favorable response to penicillin aerosol therapy. As in the treatment of asthmatic patients, there were recurrences due to either reinfection or possibly inadequate therapy.

RESULTS OBTAINED BY THE PROPHYLACTIC APPLICATION OF PENICILLIN AEROSOL

Twelve patients who were subject to disabling illness following respiratory infection were treated prophylactically during the initial or virus phase of an acute upper respiratory infection, or a "cold." These included patients suffering from asthma, as well as patients subject to repeated and prolonged attacks of bronchitis, bronchiectasis, sinusitis, and one patient with a recent history of rheumatic fever. It was reasoned that if penicillin aerosol therapy was administered during the virus phase, thereby preventing the bacterial phase from occurring, the complications of the common cold (due to bacterial infection) would be avoided. This proved to be the case in all of the 12 patients treated.

Although the cases reported are too few to draw definite conclusions, we believe that this is a definite step forward in the prevention of disabling disease due to respiratory infection. It may prove to be a valuable step in the prevention of infective asthma.

The treatment (which consisted of three daily inhalations of 100,000 units of penicillin in propylene glycol, utilizing the breathing box) must be administered at the first sign of a true "cold." It may be difficult at times to differentiate between an allergic reaction involving the nose and the common cold; rhinorrhea, nasal obstruction, and sneezing are common to both. When the patient complained of malaise, had fever, and the mucous membrane of the nose and throat were injected, the diagnosis of an acute upper respiratory infection was indicated and therapy was instituted. When in doubt, nasal smears are helpful in differentiating allergy from infection.[19]

CONTROL STUDIES

In an attempt to evaluate fully the effectiveness of penicillin aerosol administered together with propylene glycol and steam, it was important to study the effect of each separately on asthma. Previous observations with steam had indicated that a number of patients benefited, although slightly; some were made worse, due to intolerance to steam; while others were unaffected by this treatment as measured by vital capacity changes following treatment.[20]

Propylene glycol control studies were conducted in two ways. Seven patients with upper respiratory infections, previously treated successfully, although temporarily, with combined penicillin-propylene glycol aerosol, were retreated with propylene glycol alone after return of nasal symptoms. Four patients believed the treatment effective; three had negative results. No bacteriologic studies were made.

In view of the self-limitation of the acute conditions, as well as the small number of cases treated without bacteriologic studies, no conclusions can be drawn on the effectiveness of propylene glycol alone in the treatment of upper respiratory infections.

In additional control studies with propylene glycol, seven patients with severe asthma (Grade III) not previously treated with any aerosol were given five daily treatments of 20 c.c. of propylene glycol aerosol, utilizing the breathing box. Only one patient reported improvement. Two were hospitalized shortly thereafter because of *status asthmaticus*. The remainder showed no change. It would seem, therefore, that the glycol had little effect upon the asthmatic state.

REACTIONS TO AEROSOLS EMPLOYED

No serious untoward reactions were observed in the treatment of these patients with the various medicated aerosols employed in this investigation. In two instances there was mild and temporary hemoptysis in patients suffering from bronchiectasis, when sodium sulfadiazine aerosol was employed. This solution is alkaline and irritating in some instances. Buffered sodium sulfacetamide is preferable.

Penicillin in aerosol form has produced few reactions. There were two instances of mild generalized erythema. In two patients localized dermatitis about the nose and mouth developed when utilizing the breathing box—possibly due to the combined action of steam and penicillin. No serum disease-like reactions to penicillin aerosol were noted.[21]

DISCUSSION

Penicillin administered in aerosol form has decided advantages in the treatment of respiratory infections as compared with parenteral or oral administration. It brings the penicillin in concentration where it is needed most, and yet sufficient penicillin can be absorbed into the blood stream to make the attack on infection twofold—local and systemic. In respiratory infection, penicillin aerosol may even be effective where the parenteral route has failed.[22]

Failure of penicillin aerosol to reduce infection during active asthma, assuming the presence of penicillin-sensitive organisms, may be largely due to failure to inhale sufficient aerosol for effective action, because of the diminished vital capacity associated with the asthmatic state.

Chart I illustrates the effect of the reduction of vital capacity upon the absorption of penicillin aerosol as determined by penicillin blood levels. One patient, a male, 36 years old, subject to asthma, was treated with 100,000 units of penicillin in propylene glycol during an asthma-free period, utilizing the breathing box. The vital capacity at this time was 4,800 cubic centimenters. Blood specimens at one half hour and two hours, following the onset of treatment, revealed penicillin blood levels of 0.25 and 1.25 units, respectively. Several days later an attack of asthma was precipitated in this patient by violent exercise, at which time the vital capacity was reduced to 2,200 cubic centimeters. Treatment was instituted at this time, giving the same dose of penicillin

in the same manner, and blood specimens were taken again at one-half hour and two hour intervals, resulting in penicillin blood levels of 0.125 and 0.062 units, respectively. Thus, a reduction in the vital capacity by approximately one-half resulted in a reduction of penicillin blood level to 1/20 of the initial level as determined at the two hour interval.

It was, therefore, logical to employ aminophyllin and ammonium chloride aerosols to overcome bronchial spasm, and to liquefy the mucous plugs, thereby increasing the vital capacity and making the succeeding penicillin aerosol more effective.

The observations recorded here unquestionably show that penicillin aerosol is effective in many instances of infection associated with allergy. In too many instances (27.6 per cent of asthmatic patients) however, the relief obtained was temporary in nature. That this was not due to development of penicillin resistance of the organisms present was demonstrated by the good results obtained from a second or third course. Possibly, these recurrences may have been due to inadequate therapy, but the possibility of reinfection must be considered.

Negative response to penicillin aerosol therapy was probably due to a variety of factors—incorrect diagnosis (overestimating infection and underestimating the role of allergy, particularly to pollen), the presence of organisms not responsive to penicillin, intolerance of steam, and the irreversibility of some of the lung pathology in the more severe and chronic cases of asthma (marked emphysema, pulmonary fibrosis, and bronchiectasis).

Treatment should, therefore, be individualized. Penicillin, sulfonamides, and possibly streptomycin, in combinations of aerosols, should be more effective for the mixed infection commonly present in the respiratory tract. Where possible, the type of aerosol used should be determined by the bacteriologic studies of the bronchial secretions.

It should be emphasized, in conclusion, that aerosol therapy in the treatment of allergic patients is not designed to replace the accepted procedures employed to determine specific sensitivity, or elimination and specific therapy. Penicillin and other antibiotics can only be of use in overcoming infection present at the moment.

SUMMARY

1. Steam-generated aerosols of penicillin have been found useful in the treatment of infections associated with allergy, i.e., infective asthma, bronchiectasis, bronchitis, and sinusitis. The relief obtained, however, is frequently temporary in nature.

2. The use of propylene glycol for stabilizing the aerosol, and the application of various methods of conserving the aerosol, such as a chamber, tent, and breathing box, are described.

3. The prophylactic application of penicillin aerosol in infective asthma and chronic respiratory infections is illustrated.

4. The importance in *status asthmaticus* of preliminary treatment with aerosols of aminophyllin and/or ammonium chloride, prior to penicillin aerosol therapy is emphasized.

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DISCUSSION

DR. LEO H. CRIEP (Pittsburgh, Pa.).—The paper which was just presented represents a tremendous amount of clinical investigation and observation. The authors have devised and popularized a therapeutic procedure which deserves careful consideration.

One naturally wonders whether the delicate lung tissue can be subjected over long and indefinite periods of time to exposure to all sorts of drugs and chemicals without irritation, but at the present, at least, there is no obvious evidence that any damaging effect may result from such exposure, and introduction of substances like aminophyllin, penicillin, ammonium chloride, and others, although Dr. Benson's paper seems to throw a little doubt on this statement.

There is also, of course, the possibility of sensitization to sulfonamide and penicillin, and for this reason these drugs should not be used promiscuously, and I am sure everyone who has used penicillin aerosol has had cases of such sensitivity to penicillin.

The authors' statement or assumption that most all cases of *status asthmaticus* are infectious may be open to challenge.

The therapeutic results obtained by the authors in such stubborn and resistant instances as chronic asthmatic bronchitis with and without bronchiectasis, and in nasal allergy with purulent postnasal drip, is striking, especially in view of the difficulty which most of us have experienced with these cases, although careful analysis of recurrences and length of interval of observation would bear closer scrutiny.

I am interested to know how the penicillin aerosol reaches the sinuses through the narrowed and inflamed ostia, or do the authors believe that improvement in these cases comes about through the raising of the penicillin blood level? I am also interested to know whether these cases of *status asthmaticus* have responded to aminophyllin and penicillin aerosol after other forms of therapy have proved ineffective.

This form of therapy seems also effective, we hear, in the prophylactic treatment of colds by attacking the secondary invaders. Are the authors of the opinion that culturing the secretions on the surface of mucous membrane represents the true bacteriolgic condition in the deeper layers of those membranes?

The conclusions expressed I am sure are but tentative, for I understand that the authors are engaged in further studies, the purpose of which will be to enlarge the present series of patients and include also extensive controls.

The authors should be congratulated on stimulating interest in a procedure which may have wide therapeutic application.

DR. PRIGAL (New York, N. Y.).—I want to thank Dr. Criep for his discussion, and to answer him concerning the questions that he raised.

First, as to lung damage from aerosol therapy. I believe that in two instances I observed possibly some damage to the lung. This occurred following inhalation of sodium sulfadiazine aerosol. These patients were suffering from bronchiectasis, and complained of hemoptysis following this treatment. When the sulfadiazine was discontinued, the hemoptysis disappeared. Buffered sulfacetamide can be used, however, in high concentration without any irritation to the mucous membranes—solutions as high as 40 per cent have been used as eye drops.

As for adverse reactions due to sensitization, we have seen both local and systemic reactions. These have been infrequent and relatively mild. Some are in the form of a local dermatitis at the site of application of the mask. Systemic reactions result in erythema or urticaria.

We agree with Dr. Criep that infection is not the sole cause of *status asthmaticus.* What we did state, and should reiterate, is that the most common cause of *status asthmaticus* is infection.

How penicillin combats infection in the sinuses cannot be answered specifically at this time. It may be due to local deposition, to systemic action, or to both.

As for the relationship of surface culture to the actual causative agent in the production of disease, I cannot be sure that there is always such a relationship. There is presumptive evidence of such a relationship, because frequently following therapy and disappearance of the organism initially isolated there is symptomatic relief as well.

Original Articles

PERSONALITY FACTORS IN "ALLERGIC" DISORDERS

JOHN H. MITCHELL, M.D., CHARLES A. CURRAN, PH.D., WILLIAM F. MITCHELL, M.D., IOLA SIVON, M.D., AND RUTH MYERS, B.S., COLUMBUS, OHIO

FROM our earliest contacts with patients suffering from allergic manifestations there were those whose symptoms could not be explained or understood. We applied the usual diagnostic procedures used in allergy, and yet over and over again there was always a considerable percentage in whom we failed to obtain any convincing evidence of specific hypersensitiveness. As time went on and more and more of these patients were seen, it became quite frustrating. While taking the history the realization would come that the patient was going to fall in one of two groups. If he gave a concise and rather typical allergic history it could be anticipated that the skin tests would be positive; while the patient who suspected all sorts of foods, dusts, odors, and fumes as the cause of his trouble and, in addition, was very anxious to discuss in detail a great many other symptoms and complaints which did not seem to be related to the chief complaint, would usually be a nonreactor. After years of sincere effort in applying allergic methods, such as elimination diets, environmental control of allergens, nonspecific therapy, etc., to these atypical nonreacting patients, it seemed quite probable that there were other explanations than allergy to be sought for. Of course, there was always the hypothetical possibility that some undiscovered antigen would explain these cases and yet it seemed improbable that such a large number could be due to a single allergen or even a group of allergens.

It became more and more apparent that there was a basic difference between the two groups. One of us (J. H. M.) recalls pointing out to medical students that the non-reacting allergic patient seemed to have a different personality and was a very difficult problem for the physician not only from the point of view of therapy, but also in the doctor-patient relationship. These patients seemed to draw unreasonable conclusions about the causes of their symptoms, often declaring that treatment made them worse, that medicines of any sort always acted differently on them, frequently having the opposite effect from that which was expected pharmacologically. Many types of therapy were used and, although one occasionally saw apparently spectacular improvement, there was no method which afforded any consistent results.

It seemed that the problem was not being solved by a search for new allergens or new drugs and that a basic re-evaluation must be made of the generally accepted allergic etiology of the group in question. Consequently, we began to try new methods of approach. A rather thorough research pro-

gram has been established, and we have already acquired what we feel is a rather significant amount of data. A preliminary report setting forth in general our clinical impressions, without statistical data, has been published.[1] In this short paper we wish to present two limited studies which fit into a much broader series of studies, unpublished as yet, which we have made on this question.

First, 600 consecutive cases of representative types of allergy were arranged according to sex and the age when the patient came to us for treatment, as shown in Table I. Ragweed hay fever and perennial extrinsic asthma gave positive skin reactions by the prick method which could be correlated with proved causative factors, and for this reason were classified as the allergic group (Group A). Perennial vasomotor rhinitis, intrinsic asthma, and chronic urticaria failed to show positive skin reactions and were placed in the nonreactor group (Group VM). Atopic eczema also fell into this group, since positive skin reactions when encountered could seldom be proved of etiologic significance. From Table I it can be readily observed that, although there are slightly more males than females in Group A, the incidence is approximately equally divided between the sexes. Contrast this with Group VM where there is a consistent predominance of females (2:1) over males, and the symptoms are most common during the third, fourth, and fifth decades. In Group A, the majority were in the first, second, and third decades. Although atopic eczema occurs as frequently in boys as in girls in the first decade, there is a sharp deviation to females beyond 10 years of age.

TABLE I. COMPARISON OF ALLERGIC AND NON REACTOR GROUPS

	GROUP A				GROUP VM							
	RAGWEED HAY FEVER		PERENNIAL EXTRINSIC ASTHMA		ATOPIC ECZEMA		PERENNIAL VASOMOTOR RHINITIS		"INTRINSIC" ASTHMA		CHRONIC URTICARIA	
AGE (YEARS)	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0- 9	9	3	20	14	31	36	6	5	12	9	0	0
10-19	10	11	16	6	3	15	7	6	1	4	1	7
20-29	16	14	11	10	2	8	4	14	4	9	7	24
30-39	9	10	4	5	1	2	5	25	3	17	8	12
40-49	7	3	2	5	0	2	6	10	10	11	7	18
50-59	4	2	5	0	0	0	2	6	0	12	7	7
60-69	0	1	1	1	0	0	1	3	2	6	1	1
70-79	0	1	0	0	0	0	0	0	0	0	0	0
Total	55	45	59	41	37	63	31	69	32	68	31	69

There seems to be no explanation for these variations on the basis of allergy, yet such deviations in age and sex seem to indicate a fundamental difference in the nature of the two groups. One can speculate as to what the real difference is. Women in the 20- to 50-year-old age group are subjected to all sorts of pressures and difficulties; they are the least secure in our society. It is the woman that has to do the most adjusting in marriage. Confusions and conflicts concerning whether or not to have children and how much time and attention to devote to them, fears of infidelity on the part of the husband, and tensions created by well-meaning in-laws often induce apparently unsolvable situations. For the un-

married woman, life situations may be even more trying. Personality conflicts in office, factory, or schoolroom create pressures which may build up from year to year. More and more working women are forced to compete with men. The insecurity which accompanies the anticipation of growing old alone is quite threatening to many women. Fear of the loss of physical attractiveness, the psychological significance of the menopause, are each enhanced for women by the many demands which our society makes on their keeping a youthful appearance. The most common sources of conflict can be traced to difficulties in personal relationships within the home circle which have usually been conditioned by childhood experiences.

With these possible psychological factors in mind, we began to investigate the personal problems of these patients. Of great aid were two books on modern psychotherapeutic techniques by Rogers[2] and Curran.[3] Many in Group VM made statements of confusion, conflict, hostility, fear, family or office trouble, guilt feelings, and social inadequacies in relating their case histories. More and more evidence pointed to the fact that the allergic symptom was but a part of a broader psychosomatic picture in the nonreacting groups. This realization has proved most helpful in diagnosis and in our therapeutic approach, and we are able to help many patients who previously would have drifted away and been classified as failures in allergic management. The increasing success of this point of view in facilitating our approach to patients has given further impetus to the research we have been doing.

Our second observation is taken from our findings on patients complaining of "year around asthma." A total of 1,129 cases seen in private practice from 1934 to 1944 were classified according to the major etiologic factor as shown in Table II. In about one-half (48.5 per cent) we find the typical allergic pattern with positive skin tests and proved extrinsic allergens. Recurring bronchial infections accounted for 14.5 per cent, and miscellaneous anatomic and structural changes accounted for approximately 12 per cent. There remained 255, or 22.7 per cent, where all diagnostic procedures failed to give any clue to the cause. In other words one out of every five patients over a ten-year period, despite our best efforts, was turned away physically no better than when he came. We were, according to our own records, completely at a loss, not only as to possible therapy, but also as to the causes of the illness.

We have recently examined 100 consecutive cases of the same type of "year-around asthma" and, as will be noticed in Table II, the same general classifications of these cases were numerically almost identical in percentage with the cases of the previous ten years. But by this time we were quite aware of possible psychogenic causes and personality problems and were allowing patients to discuss freely whatever problems they cared to without limiting the time consumed in giving the history and without rejecting as unreasonable whatever statement they made about possible causes. If the time extended beyond one-half hour, the patients were invited to return again for another or, if necessary, a series of interviews. The table shows a remarkable correlation between these cases and those seen in the previous ten-year period. Of the 100 cases, 21 per cent were considered psychologically maladjusted in view of the expressions of

confusion, hostility, fear, guilt feelings, etc., which were made in the initial history interview. In other words these people, when allowed to talk, by their own statements showed what was to us an amazing picture of personality problems and confusions. And this in sharp contrast to the usually clear-cut succinct, unemotional statements which were common to the other diagnostic groups.

TABLE II. CLASSIFICATION OF PATIENTS WITH "YEAR AROUND ASTHMA"

	1934 TO 1944		1945
	1,129 CASES	PER CENT	100 CASES
Extrinsic: dusts, animals, etc.	559	48.5	44
Recurring bronchitis	164	14.5	14
Fixed emphysema	75	6.6	11
Aspirin	32	2.8	2
Cardiac	13	1.1	6
Bronchiectasis (proved)	18	1.6	2
Sighing dyspnea	6		0
Tuberculosis	3		0
Tumors: benign	1	1.1	0
malignant	2		0
Foreign body	1		21
"Cause not determined"	255	22.7	(psychologically maladjusted)

It seems highly probable now that had we known how to recognize maladjustment, the majority of those 22.7 per cent previously classified as "cause not determined" would have been classified as psychologically maladjusted. We wish to point out that in classifying these cases the object was to emphasize major aspects of differentiation. That characteristic differences do exist between Groups A and VM we hope to show in later papers. Individual patients, however, may manifest characteristics of both groups, and so in diagnosis and in treatment it is necessary to evaluate both the physical and the psychological aspects. Maladjustment as a major component is encountered in a high percentage of Group VM patients, while the incidence in Group A is much lower.

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FLOUR ALLERGY*

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EVERYBODY is daily exposed to the more or less injurious influence of allergens; some individuals are sensitized to one or several of these substances, but very few incur clinical symptoms of allergic affection.

In certain industries the influence of allergens is very great, and if the action of an allergen is strong, the number of both sensitized and clinically ill individuals may reach 100 per cent, as is observed, for example, in certain persons working in nickle-plating factories, where all are affected with eczema.[24]

For many years it has been known that bakers, millers, and other persons who are occupied in an atmosphere filled with grain-dust often are attacked by bronchial asthma or other allergic diseases. Baker's asthma, baker's coryza, and baker's eczema within the industry are reported to be between 10 and 23 per cent,[3, 11, 16, 23] and since the affected persons often are disabled for long periods and not infrequently are compelled to leave their trade, it is understandable that this is a disease of no little social and economical importance.

PREVIOUS INVESTIGATIONS

Sensitization with flour, grain, or products thereof might be assumed to be effected orally as well as by inhalation and contact. Flour allergy incurred by others than bakers, millers, and grocers being rare, peroral sensitization may be disregarded here. Then sensitization as well as the causation of symptoms is, therefore, due largely to inhalation and, particularly as regards eczema, to contact with the allergens.

The affections in question are bronchial asthma, vasomotor rhinitis, and eczema, urticaria being observed very rarely.

BRONCHIAL ASTHMA AND VASOMOTOR RHINITIS

Each of these affections may be present separately, or they may both appear at the same time; or vasomotor rhinitis (flour coryza) may, after a shorter or longer lapse of time, be followed by bronchial asthma—in fine analogy with the pollinoses which may manifest themselves as hay fever, asthma, or both these affections.

That bakers frequently are sensitized to flour—evidenced by positive cutaneous reactions with extracts of flour—was shown by Berger[4] and by Schmidt,[25] and in 1929 de Besche[5] introduced the idea that "baker's asthma" is an allergic industrial disease.

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The first to establish that flour allergy was most commonly seen in bakers was Baagøe[3] who in 1933 collected 17 cases of "clinical idiosynerasy opposite flour dust," 15 of the 17 patients being bakers. Besides his own 17 cases Baagøe collected 17 cases from the literature.

Subsequent greater investigations have shown that from 10 to 70 per cent of bakers and millers present positive cutaneous reactions with extracts of the different kinds of flour, and that a somewhat smaller number—from 10 to 23 per cent—suffer from clinical flour allergy.[3, 9, 11, 16, 23, 29] Positive cutaneous reactions without clinical allergy (latent allergy) are thus not rare,[23] negative cutaneous reaction on the contrary is uncommon in clinically affected persons (Dishoeck and Roux[10]).

All degrees of the disease may be seen, from insignificant coryza and sneezing or a little cough and wheezing during the dustiest work, up to violent, day-long attacks after merely a few minutes' stay on the premises. The asthma usually causes the patients the greatest distress, but vasomotor rhinitis may also become so violent that the disease compels the patient to leave his work (*Hlavacek*[16]).

ECZEMA

This affection will be discussed but briefly, because it is not in the scope of this investigation. The subject has recently been treated in detail by *Bonnevie*.[6]

The affection is met with particularly in bakers, and in most cases it is localized to the hands and forearms, those parts of the skin which are especially exposed to contact with flour. The etiology of baker's eczema is much more varied than is supposed to be the case with baker's asthma and coryza.

A number of different substances added to the flour in order to improve its appearance and baking efficiency are described as causes of baker's eczema (*Bonnevie*[6]), and those substances may vary from one country to the other and change in the course of time.

However, pure flour may give rise to eczema,[6, 10, 19] and bakers with eczema very often are sensitized to flour.[25, 28] Possibly a flour allergy may give rise to exacerbation of an eczema of another etiology by causing "spontaneous scratch tests" in the eczema lesions (*Bonnevie*).

The frequency of baker's eczema in a mixed material of bakers and millers was 18 per cent.[11]

THE WRITER'S OWN INVESTIGATIONS

In the allergy dispensary of the medical outpatient department, 35 persons with flour allergy (24 bakers, 2 millers, 7 confectioners, a woman working in a biscuit factory, and a miller's son) were examined and treated during the last two and one-half years.

All the patients were submitted to the ordinary clinical examination; in the majority of the cases x-ray examination of the lungs (all the asthma patients) was performed and, in older patients, electrocardiography.

Cutaneous reactions with about 60 different allergens were tried on all the patients, in a few cases as scratch tests, and otherwise as intracutaneous tests. Moreover, intracutaneous reactions with extracts of different kinds of flour (oat, rye, wheat, barley, and "mixed flour" (rye and wheat) were tried on all the patients. Twelve were submitted to intracutaneous reaction with a $\frac{1}{10}$ per cent aqueous solution of potassium bromate (which is used for the improvement of the baking efficiency) and with a $\frac{1}{10}$ per cent aqueous solution of monochloramine (which is used for bleaching the flour).

In all the cases the diagnosis of flour allergy was made on the past history in connection with the cutaneous reactions. The great majority of the patients declared that flour was at the bottom of their affections, and we have observed no case, which clinically was interpreted as flour allergy, that did not react positively to extracts of one or several kinds of flour.

The extracts were made by P. T. C. Barfoed (dispensing chemist of the Frihavnsapotek, Copenhagen) who employed the ordinary merchandise (wheat-meal, rye-meal, etc.), which by frequent microscopical examinations was found to be free from mites, larvae (grub), remains, or other pollutions. All the extracts were tested thoroughly on normal persons, where they were always found to be inactive.

DISCUSSION

Etiology.—All our patients were working in occupations, where they were exposed to flour dust or grain dust. All reacted positively to intracutaneous injections of extracts of one or several kinds of flour, and almost all of them believed flour responsible for their symptoms. That does not prove, however, that flour (the flour proteins) per se is the specific etiologic factor.

Flour and grain may be polluted in different ways. Moreover, the ordinary merchandise as a rule is treated with different chemical substances, i.e., partly bleaching substances, partly the so-called "flour-improving" substances. Such substances might be considered to give rise to the symptoms.

In 1922 *Ancona*[1] described a number of cases of asthma observed among laborers in an Italian mill. All were affected, and as cause of the symptoms *Ancona* found a mite (*pediculosus ventricosus*) with which the grain in the mill was strongly polluted. An extract of the mite gave strong positive cutaneous reactions (scratches), whereas the cutaneous reactions with the clean grain were negative. Later investigations by *Grove*[13] showed, however, that the infected grain gave rise to pronounced local irritation, and, since it proved impossible to demonstrate circulating antibodies, the allergic etiology of *Ancona's* cases was questioned severely; at any rate this was an exceptional case.

As regards flour proteins[3, 6, 23] it generally is easy, even in cases of mere latent allergy,[23] to demonstrate circulating antibodies, "reagins," the presence of which is considered to be reliable proof of an allergic condition.

The samples of flour which we employed for preparing the extracts were always free from pollution with mites or microorganisms, nor were there found any remains of chaff which were described as cause of allergic symptoms in

millers (*Duke*[12]). We, therefore, think that these factors may be excluded. It has been shown that extracts of pure grain do not give any cutaneous reactions in patients who react to mites.[23]

In the course of time a great number of substances have been added to the flour in order to increase its baking efficiency, and the natural, generally yellowish color of the flour has been bleached with the help of decolorants. These substances, which frequently give rise to baker's eczema, have been considered to be the cause of baker's asthma and baker's coryza too.[6, 7, 15, 19, 29, 30]

The substance employed almost exclusively during recent years for improving the baking efficiency of the flour (since ammonium persulfate was prohibited in Denmark in 1936) is potassium borate[18]; the bleaching substances which are used particularly are benzoylsuperoxide and monochloramine.[18] These may give rise to eczema in bakers, but certainly only in extremely rare cases to asthma or vasomotor rhinitis. Only one single case of asthma due to ammonium persulfate[29] is on record in the literature against many thousand cases of eczema caused by this substance.

We have examined 12 of our patients with intracutaneous injections of aqueous solutions of potassium bromate ($\frac{1}{10}$ per cent) and monochloramine (1 per cent)—benzoylsuperoxide not being soluble in water, it is not appropriate for intracutaneous injection.

Readings were made after the lapse of fifteen minutes. Patch tests were not performed (Table I).

TABLE I. INTRACUTANEOUS REACTIONS IN FLOUR ALLERGICS

	+	−
Sorts of grain (23 patients)		
Oats ($\frac{1}{10}$ per cent)	23	0
Rye ($\frac{1}{10}$ per cent)	22	1
Wheat ($\frac{1}{10}$ per cent)	19	4
Barley ($\frac{1}{10}$ per cent)	18	5
Potassium bromate and monochloramine (12 patients)		
	+	−
Potassium bromate ($\frac{1}{10}$ per cent)	6	6
Monochloramine ($\frac{1}{10}$ per cent)	5	7

It will be seen from Table I that a certain sensitization to those substances does ensue, but it scarcely is of importance for the allergic affection of the organs of respiration.

In this connection eczema and urticaria met with in our patients shall be mentioned. Four patients at the moment of examination presented eczema located to the hands. In one case only was the affection so pronounced that it required special treatment; five other patients reported that they had previously had eczema; two of these thought that the affection had occurred synchronously with the addition of ammonium persulfate to the flour, and had disappeared with the prohibition of its use.

One patient, i.e., the one who suffered from pronounced eczema, incurred urticaria when a little piece of dough happened to stick to his skin. A similar case was previously observed by Baagøe.

The Importance of the Several Kinds of Flour.—All our patients had been working with more than one kind of flour, most of them particularly with rye and wheat-meal.

Twenty-three patients were submitted to intracutaneous reactions with all the four kinds of grain (wheat, oats, barley, and rye). The concentration of the extracts applied was $\frac{1}{10}$ per cent in all the cases, but most of the patients were tested with other concentrations. The results are shown in Table I.

It is peculiar that oats, with which the patients had been in least contact, gave the greatest number of positive reactions. It has been shown[23] that bakers mostly are sensitized to that kind of flour with which they mostly work, but there is considerable overlapping. Whether that is due to a common antigen or whether it is the result of polyvalent sensitization is difficult to decide, since the patients in almost all the cases have been in contact with several kinds of flour.

The Importance of Disposition.—Here, disposition means, partly, the occurrence of allergic inheritance and previous or present allergic diseases in the patient himself, which cannot be attributed to grain- or flour-dust.

Sixteen (46 per cent) of the patients reported that allergic diseases occurred in their families, and two others were allergic to other substances than flour (one to pollen, and the other to cat). The number of flour allergics with allergic disposition was thus 52 per cent. A single investigator,[16] on testing 70 bakers, found that only the hereditarily tainted were sensitized. *Baagøe*[3] finds, just as we do, that about one-half the patients have allergic dispositions, whereas *de Besche*[5] found that only one out of 7 patients with flour allergy had a disposition to allergic affections.

Three of our patients (8.5 per cent) had typical hay fever during the season. That evidently is no contingency, for other investigators[10, 11, 23] find that up to 44 per cent of the flour allergics react to pollen. On the other hand, hay fever patients are reported not to be very hypersensitive to flour, *Dishoeck and Roux*[10] reporting six flour allergics among 70 hay fever patients.

The Sensitization Time.—The time elapsing between the moment the patient is exposed for the first time to the allergen and the appearance of the first symptoms varies extraordinarily, namely, from a few weeks to more than 35 years; in those cases in which the patients suffer from asthma and vasomotor rhinitis the time of sensitization is calculated from the inception of that of the two affections which has occurred first. Sensitization time really ought to mean the time elapsing between the moment the patient for the first time is exposed to the allergen and the moment when the cutaneous reaction becomes positive; in this material, however, the latter moment could not be determined.

The average sensitization time of our patients is 10.8 years. *Baagøe*[3] found eleven years for his 15 bakers, and *de Besche*[5] found fifteen and eight-tenths years for his five patients. In six cases the patients' fathers had been bakers (32 of them were interrogated about it). Thus, to a certain degree, the profession is "inherited." Two patients (millers) reported that they had

frequented the bakery as children, whence it was difficult to determine their sensitization time. The remaining four patients did not think they had been particularly in contact with flour before they were apprenticed at the age of 14 years.

In those patients (twenty-three) who have had both asthma and vasomotor rhinitis, the average sensitization time for vasomotor rhinitis was 8.4 years against 13.2 years for bronchial asthma. Vasomotor rhinitis precedes bronchial asthma; in 12 cases the patients had suffered from vasomotor rhinitis for a shorter or longer period before they incurred asthma, and we have in no case observed that asthma preceded vasomotor rhinitis (Table II).

TABLE II. DIAGNOSES AND SENSITIZATION TIMES OF 35 FLOUR ALLERGICS

DIAGNOSES	NUMBER OF PATIENTS	SENSITIZATION TIME
Bronchial asthma + vasomotor rhinitis	23	br. asthma 15.8 years vas. rhin. 8.4 years
Bronchial asthma alone	10	15.7 years
Vasomotor rhinitis alone	2	11.0 years

The sensitization time being considered, together with the disposition to allergic diseases, it is found that the 18 patients with allergic disposition had a sensitization time of 11.3 years against 11.2 years found for the patients without disposition. Thus the disposition plays no rôle for the sensitization time.

The Duration of the Sensitization.—This form of allergy is described as being very constant, possibly enduring throughout the patient's lifetime[10]—in contradistinction to ammonium persulfate allergy, which is of shorter duration. One of our patients who has not been working for six years still develops symptoms as soon as he stays in a bakehouse for but a few minutes. We have treated another patient who now, i.e., twenty years after having given up his work as a miller, constantly presents strong cutaneous reactions to injections of flour extracts.

The Correlation Between Symptoms and Work.—The majority of our patients incurred symptoms only during work, being symptomless a couple of hours after having left it. This holds for all the cases of vasomotor rhinitis. In some cases (20 per cent) the patients incurred attacks at any time of the day, and frequently at night. The character of the work and the arrangement of the workshop play an important role. The more dust there is in the workshop the greater will be the number of persons who are sensitized and incur symptoms. It has been shown that 44 per cent of the bakers in small establishments are sensitized against 25 per cent of the workmen in the larger, more hygienically arranged bakeries.

Many of our patients (23 per cent) did not incur severe symptoms until the introduction of black-out in 1940, and they attributed them partly to the inferior ventilation during black-out, whereas a few patients emphasized that the "war flour" gave off more dust.

Certain parts of the working process give off more dust than do others, for example, "flour-throwing" and kneading; fancy bakers are not exposed to

nearly so much flour dust as the workmen in the large rye-bread factories. Many persons who are unable to work in ordinary bakehouses manage quite well as confectioners.

In some cases the patients noticed that their symptoms appeared or exacerbated considerably immediately after their having resumed their work which had been interrupted for some time. Valléry-Radot and Blamoutier[27] in several cases observed the same phenomenon; that may possibly be interpreted as the expression of latent allergy, the symptoms of which before the interruption of work were kept down by constant spontaneous sensitization due to the influence of the allergen in the workshop.

Rowe,[21] in this connection, emphasizes that clinical allergy frequently does not occur before the patient is quite "clear" of the allergen and meets it again. Other authors report, however, that flour allergics tolerate the work better after a short vacation.[8]

TREATMENT

The most effective procedure in allergic affections certainly is the patient's removal from the allergen or vice versa. In practice this is feasible only when the patients leave their trade; in isolated lighter cases they will manage as confectioners. Masks are an excellent theoretical solution of the problem, but they are so uncomfortable in practice that the patients as a rule prefer the symptoms to them. A temporary removal in our experience never seems to bring about any lasting improvement of the condition. On the contrary, after an absence from work the patients may incur an exacerbation of their symptoms.

The symptomatic treatment (with adrenalin, ephedrine, etc.) will not be discussed in detail. The rational treatment should be specific desensitization with extracts of those kinds of flour which the patients do not tolerate.

This treatment has been used by several authors[14, 16, 17, 26, 27] on a fair number of patients, and the results on record are very different, varying between no effect at all[27] and improvement in 89 per cent of the cases.[17] The treatment as a rule consisted of subcutaneous injections of increasing quantities of a flour extract, and in isolated cases of submucous injections in the nasal mucosa.[14, 26]

Besides specific desensitization, large doses of vitamins (A and D)[20] and repeated small venesections[27] were recommended; an explanation of the eventual mechanism of action of these methods of treatment has not been given.

Thirty of our 35 patients were treated with specific desensitization; no other treatment was applied. The patients took their usual symptomatic remedies.

The treatment consisted of subcutaneous injections of increasing quantities of allergen—generally in the form of an extract of that kind of flour which gave the strongest cutaneous reaction. The period of treatment varied somewhat, all the patients receiving treatment for at least six weeks, most of them much longer (6 for one to two months, 11 for two to three months, 7 for three to four months, and 6 for more than four months).

Apart from moderate local reactions, the treatment did not give rise to discomfort, nor were there observed any cases of allergic shock.

The results are recorded in Table III.

TABLE III. RESULTS OF TREATMENT (SPECIFIC DESENSITIZATION) OF 30 FLOUR ALLERGICS

	NUMBER OF PATIENTS	SENSITIZATION TIME (AVERAGE)	DURATION OF DISEASE (AVERAGE)
Symptomless	3	13.6 years	12.0 years
Improved	8	11.1 years	7.2 years
Unchanged	19	10.5 years	11.4 years

The observation time was at least one year. As is seen, the results are inferior to those generally obtained in asthmatics in Denmark (*Bruun*[8]). Only those patients were regarded as improved who experienced a doubtless improvement persisting for at least three months; if a persistent recidivation occurred after a couple of months, the case was regarded as being unchanged. Patients quoted as being unchanged often were treated for a particularly long period and very intensely. Thus the bad results in those cases is not due to underdosage.

It might be thought that the therapeutic result depended upon the length of the sensitization time so that the rapidly sensitized patients on desensitization would obtain the best prognosis. That does not seem to hold, however, since the average sensitization time for the three groups—symptomless, improved, and unchanged—was 13.6 years, 11.1, and 10.5 years, respectively.

It is reported[22] that the therapeutic result of specific desensitization is best, if the treatment is commenced as soon as possible after the onset of the disease. With regard to this group of patients that cannot be decided with certainty, for at the commencement of treatment of the three groups—symptomless, improved, and unchanged—the disease was of 12.0, 7.2, and 14 years' standing, respectively.

Eleven (38 per cent) of the patients have profited by specific desensitization. That certainly is no very brilliant result, but nevertheless it invites continuation in the same way. About the results after the lapse of more than three years nothing is known. A few authors[27] allege that no effect whatever of desensitization treatment of flour allergy is noticed in the long run.

None of our patients have in the course of their disease, which in many cases persisted for several years, noticed any spontaneous improvement. Therefore, we are justified in assuming that the improvement observed after the desensitization treatment is a reality, and we may hope that it will persist or that the disease, in case of recidivation, again will yield to the treatment.

Special attention should be paid to the circumstance that 8 of our 35 paitents gave up their work within the observation time, and that 7 of those 8 individuals took treatment without effect. Even though our cases were, perhaps, very severe, and the patients consulted us as a last resource, their number is strikingly high. We have received reports from all at least three months after having left the flour-dusty trade; seven of them are quite symptomless, working in other trades; but, with one exception, they all receive lower wages

than in their former trades. One is permanently unable to work, with severe dyspnea on exertion, but as he has bronchiectases, too, his condition may be explained on that basis.

According to the above it may be assumed that pronounced flour allergy is enough to compel a man to leave his trade, but that it does not generally give rise to permanent invalidism. On the other hand, it is quite as possible that several of those patients will develop allergy to other substances in other trades, many allergies being known to become polyvalent in the course of time.[22]

It is endeavored to elucidate this question by reviewing the reports of the Danish Invalidity Insurance Council for patients with bronchial asthma from 1928 to 1942, inclusively. All the cards of the card-index (annuitants, deceased, requests denied; 2,050 cases altogther, among which 1,015 were men) were reviewed. In those cases in which the individual was reported to be a baker (journeyman, master etc.), a confectioner, or a miller, the report was examined in order to obtain information concerning an eventual relationship between the disease and the trade. Fifteen patients in all were found, distributed evenly through those fifteen years, 14 received an invalid pension. The asthma of 4 of the 15 patients had no relation whatever to the work with flour, which left but 11 patients (3 millers, 1 confectioner, and 7 bakers).

The number is very small, and it confirms our supposition that permanent invalidism as a consequence of flour allergy is rare.

During the period from 1928 to 1942, inclusively, 1,654 persons altogether received an invalid pension on account of bronchial asthma (806 of them being men).

The Prophylaxis.—The sensitization time for these diseases being very long—10.8 years on an average—it means that a baker, miller, or confectioner frequently at a rather late moment of his life is compelled to change his trade, and since only a minor number of patients is cured by the treatment, the prophylaxis is of great importance. It is necessary, through an occupational guidance, partly to dissuade persons with allergic disposition from entering such trades, or to endeavor to decrease the allergen influence by adequate measures in the workshops.

A special examination aiming at eliminating the disposed persons was tried with regard to baker's eczema.[30] A group of baker's apprentices were submitted to patch tests in order to detect those who were exposed to eczema. Re-examination disclosed, however, that those apprentices who, despite the advice given, had tried their hands on bakery had managed just as well as those in whom the patch tests had been negative. That implies nothing, however, with regard to the eventual benefit of a similar test with intracutaneous reactions; for that test the psychotechnique institute, for example, could refer is clients, or the bakers' company its apprentices.

By means of increased mechanization of the working-process and better ventilation of the localities of bakehouses and mills, it will be possible to obtain a very considerable decrease of the flour dust.

If these measures are carried through, the number of patients with baker's asthma and baker's coryza will no doubt be reduced very considerably.

SUMMARY

1. An account is given of 35 cases of flour allergy from the allergy dispensary of the Rigshospital in Copenhagen. The etiology of flour allergy is reviewed. The importance of disposition and the long sensitization time are emphasized. The treatment consisted of specific desensitization. The results—improvement in 38 per cent of the cases—are regarded as being small, but they suggest continuation of such treatment.

2. Attention is drawn to the circumstance that flour allergy is a professional disease, and the importance of prophylaxis is emphasized.

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Editorial

Many interesting ideas and many "good" experiments have been "spoiled" by controls. How easy it is to believe that when a result follows a procedure that this result always depends upon that procedure. Propter hoc is very different from post hoc. In asthma, indeed in all the allergic diseases, the danger is greater than usual. This is not only because the nature and cause of the process is still obscure, but particularly because so many different factors can play their parts in it.

New methods of treatment are particularly open to the risk of a hasty belief in their benefit. We recall our enthusiasm when ephedrine first appeared. Aminophyllin was hailed next. Histamine, given by itself or later in protein combinations, was recommended warmly as a panacea. Now, however, we have learned of its limitations. During this past year or two the antihistamine drugs have been described, extolled, and finally relegated to their proper places. New preparations impress the doctor and they impress the patient. Incidentally, a new doctor means a fresh start and a new hope. Almost every new patient reports his asthma improved during the first period of treatment, until later he discovers that the new methods are not so fundamental after all.

New treatments are always welcomed, but none of us can afford to believe at the outset that they are perfect. They deserve to be considered carefully and used with as much intelligence and care as possible. If the controls are good, if other cases treated with placebos do not do just as well, then the truth will appear.

New theories are essential to our progress. If the theory is good, the evidence in support of it will become readily apparent and available. If, however, the theory is not so good and the evidence behind it is of doubtful value, then the further consideration of it is a waste of time. Ideas are valuable. No advances are made without them, but where the evidence is lacking or where the observations made can be explained quite as easily on some more familiar basis, publication should be withheld. When the evidence can be clarified and displayed in orderly fashion, then progress is made.

F. M. R.

American Academy of Allergy

NEWS AND NOTES

COMMITTEE REPORTS

The *Executive Committee* announces that a Research Fellowship has been established in the Department of Physiology and Pharmacology at the Graduate School of Medicine, University of Pennsylvania, with a stipend of $2,400 to $3,000 per annum. Such a fellow is to be one directed toward academic medicine and is to be known as Research Fellow of the American Academy of Allergy. Selection of such a fellow is to be made by Doctor J. H. Comroe, Jr., Professor of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania.

At a meeting of the Executive Committee on June 13, 1947, Doctor Albert Vander Veer was elected to Emeritus Membership in the Academy.

Committee on Therapy.—

This includes reports of Dr. Robert Chobot, Dr. William Schiller, Dr. George I. Blumstein, Dr. H. H. Gelfand, Dr. C. Malone Stroud, and Dr. S. S. Bullen.

PRELIMINARY REPORT ON NEO-ANTERGAN

TYPE OF CASE	DOSAGE (MG.)	INTERVAL BETWEEN DOSES	TIME OF ONSET OF ACTION OF DRUG	DURATION OF ACTION	NO. CASES	EFFECTS G*	F	P	TOXIC EFFECTS
Nonseasonal allergic rhinitis	50-250	3 to 6 a day	15 min. to ½ hr.	Several hours in effective cases	46	13	7	26	3—Sleepiness 1—Headache 1 Sore throat and dizziness
Seasonal allergic rhinitis	50-250	3 to 6 a day	15 min. to ½ hr.		27	24	2	1	1 Dizziness
Urticaria	50-100	3 to 6 a day	15 min. to ½ hr.		13	10	1	2	None
Atopic eczema	50-100	3 to 6 a day	15 min. to ½ hr.		14	2	1	11	Marked prostration. Dilatation of pupils—1 sore throat and dizziness
Pruritis of legs—six years	150-250	3 to 6 a day	15 min. to ½ hr.		1	1	–	–	None
Bronchial asthma	100-400	3 a day	15 min. to ½ hr.		18	5	2	11	1 Headache and cramps 1 Sore throat and dizziness
Pollen asthma	100-400	3 a day	15 min. to ½ hr.		8	2	0	6	None
Seasonal hay fever	100-400	3 a day	15 min. to ½ hr.		48	24	8	16	Headaches and sleepiness
Angioneurotic edema	100-400	3 a day	15 min. to ½ hr.		4	0	1	3	None
Migraine	100-400	3 a day	15 min. to ½ hr.		4	1	0	3	None
Fungus infection of skin	50-100	3 a day	15 min. to ½ hr.		1	0	1	0	None
Gold dermatitis	50-100	3 a day	15 min. to ½ hr.		1	0	0	1	None
Poison ivy	50-100	3 a day	15 min. to ½ hr.		1	0	0	1	None
Vernal conjunctivitis	100	3 a day	15 min. to ½ hr.		2	0	0	2	None

G. = good; F. = fair; P. = poor.

Announcement is made by Dr. Chobot, Chairman of the Committee, of a grant of $500 by the Bilhuber Corporation, to the Research Fellowship Fund of the Academy.

The *Committee on Public Relations* as appointed by President Spain has as its Chairman Doctor Horace S. Baldwin. A system of Regional Secretaries has been set up in order that information of interest from various areas of the country may be integrated and published in the "News and Notes" column of the JOURNAL. The Regional Secretaries with the areas in which they serve are as follows:

Dr. John L. Fromer, Brookline, Mass.—Maine, Vermont, New Hampshire, Rhode Island, Massachusetts, Connecticut
Dr. Fred Brown, New York, N. Y.—New York and New Jersey
Dr. George J. Stuart, Washington, D. C.—Virginia, W. Virginia, Maryland, Washington, D. C.
Dr. James A. Mansmann, Pittsburgh, Pa.—Pennsylvania and Delaware
Dr. Edna Pennington, Nashville, Tenn.—Kentucky, Tennessee, N. Carolina
Dr. Mason I. Lowance, Atlanta, Ga.—Alabama, Georgia, S. Carolina, Florida
Dr. Henry Ogden, New Orleans, La.—Mississippi, Louisiana, Texas
Dr. Samuel Bukantz, St. Louis, Mo.—Missouri, Arkansas, Kansas, Oklahoma
Dr. Adolph Rostenberg, Chicago, Ill.—Illinois, Indiana
Dr. Merle Fenton, Detroit, Mich.—Michigan, Ohio
Dr. Meade Burke, Madison 3, Wis.—Wisconsin, Minnesota, Iowa, N. and S. Dakota, Nebraska
Dr. Dean Moffett, Salt Lake City, Utah—Idaho, Montana, Wyoming, Colorado, Utah
Dr. William B. Steen, Tucson, Ariz.—Arizona, New Mexico
Dr. Frank Perlman, Portland, Oregon—Washington, Oregon
Dr. Hyman Miller, Beverly Hills, Calif.—California, Nevada

Excerpts from report of the *Subcommittee on Undergraduate Education** in Allergy.—A subcommittee on Undergraduate education was appointed by the American Academy of Allergy at its first meeting. The subcommittee has accomplished two of its several aims. It has formulated recommendations for a minimal Allergy curriculum, and it has surveyed the status of instruction in the sixty-six recognized medical schools.

Table I contains the recommendations for a minimal Allergy curriculum:

TABLE I. RECOMMENDATIONS FOR THE MINIMAL ALLERGY CURRICULUM

I. Instruction in Allergy should be sufficient to give each student a reasonable knowledge of:
    Anaphylaxis
    Pathological physiology of allergy
    The clinical recognition of the various manifestations of allergy
    The etiological diagnosis of allergy
        (1) History taking (2) Skin testing (3) Elimination procedures (4) Allergens and allergen sources
    Treatment of allergic diseases
        (1) Symptomatic (2) Avoidance of allergens (3) Desensitization and immunization
II. Each student should have at least 12, preferably more, hours of instruction in these topics.
III. The division of these hours among the departments of immunology, allergy division of internal medicine, dermatology and pediatrics should be left to the curriculum committees of the schools.
IV. The method of instruction (didactic, case demonstration, clinics, etc.) should conform to current practices at the individual schools.
V. Instruction in allergy should be done by men whose chief interest is in allergy.
VI. An Allergy Clinic is a prerequisite to good instruction in allergy.
VII. Elective courses should be available for those students who wish to emphasize allergy.

*Drs. Robert L. Benson, Stearns S. Bullen, Leo Criep, Samuel M. Feinberg, Leslie Gay, Robert A Cooke, Oscar Swineford, Jr., chairman.

TABLE II. UNDERGRADUATE INSTRUCTION IN ALLERGY QUESTIONNAIRE

QUESTIONS	ANSWERS		
	YES	NO	NO REPLY
1. Is there an Allergy Clinic?	57	9	--
2. Is the Clinic used for teaching?	50	6	10
3. Do all students rotate through it?	27	23	16
4. Is it elective?	21	24	21
5. Has the clinic been approved by the Advisory Board of Allergists?	23	28	15
6. Do all students have didactic instruction in Allergy?	55	6	5
7. Is clinical instruction in Allergy by Allergists?	47	19	--
8. Is there an elective course for more detailed study of the allergic diseases?	12	38	16
9. Had instruction in Allergy increased in the five years preceding the war?	36	25	5
10. Is the budget for the work in Allergy equal to that for Cardiology or Dermatology?	15	23	18
	(No budget—10)		
11. Does the school provide funds for research in Allergy?	18	42	6
12. For research in other specialties?	36	14	16
13. Do you have plans for increased undergraduate instruction in Allergy after the war?	27	26	13
14. Is there a Department of Allergy?	6	54	6
15. Does your school conform to allergy curriculum recommendations of the committee?	44	22	--
16. Are each of your students given at least 12 hours of instruction in Allergy?	31	35	--
17. Is it a subdivision of another Department? In at least 52 schools it is a subdivision of Internal Medicine. In 3 schools it is under immunology, Dermatology, Pediatrics, respectively.			

The survey of the status of instruction in Allergy was done by a series of questionnaires. Replies to seventeen questions in the questionnaires are summarized in Table II.

The individual replies of each school to four important questions are summarized in Table III. Those questions are:

1. Do you have an Allergic Clinic?
2. Are all of your students instructed in Allergy by Allergists?
3. Does your instruction in Allergy include the topics recommended?
4. Does each student have at least twelve hours of instruction in Allergy?

An analysis of Table III shows that thirty-one of the sixty-six schools seemed to have an acceptable minimal curriculum. In nine other schools the deficiencies seemed to be minor. In twelve schools there is little or no organized instruction in Allergy. In fourteen schools the instruction does not approach the recommended minimal curriculum.

It seems rather obvious that the schools which do not have Allergy clinics should start them. Instruction in Allergy should be assigned to people who are trained in this field. It is thought that a good Allergist with a well-supported clinic would soon find a logical way to conform to the recommendations for the minimal Allergy curriculum without disturbing the framework of the curriculum already in use in his school.

It is difficult to understand the discrimination which continues to deprive medical students of at least a smattering of the instruction they need to deal fairly with the ten per cent or more of his future patients who are victims of Allergy.

Clinical Allergy has been the stepchild of undergraduate medical education too long.

REFERENCE

1. Undergraduate Education in Allergy, Report of the Subcommittee on Undergraduate Education in Allergy of the American Academy of Allergy, J. Asso. Amer. Med. Col., Sept., 1946.

TABLE III. SURVEY OF UNDERGRADUATE INSTRUCTION IN ALLERGY IN UNITED STATES

SCHOOL	IS THERE AN ALLERGY CLINIC?		ARE ALL STUDENTS TAUGHT BY ALLERGISTS?		DOES TEACHING CONFORM TO OUTLINE I?		IS EACH STUDENT TAUGHT ALLERGY 12 HOURS?	
Albany M. Coll.*	Yes		Yes		Yes		Yes	
Arkansas*	Yes		Yes		Yes		Yes	
Baylor‡		No	Yes		Yes			No
Boston‡	Yes		Yes			No		No
Buffalo‡	Yes		Yes			No		No
California*	Yes		Yes		Yes		Yes	
So. California*	Yes		Yes		Yes		Yes	
Chicago*	Yes		Yes		Yes		Yes	
Cincinnati§	Yes			No		No		No
Colorado†	Yes			No	Yes		Yes	
Columbia‡	Yes			No		No		No
Cornell*	Yes		Yes		Yes		Yes	
Creighton†	Yes		Yes		Yes			No
Duke*	Yes		Yes		Yes		Yes	
Emory§		No		No		No		No
Coll. Med. Evang.*	Yes		Yes		Yes		Yes	
Georgetown‡	Yes			No	Yes			No
George Washington§		No		No		No		No
Georgia§		No		No		No		No
Hahnemann M. Coll.*	Yes		Yes		Yes		Yes	
Harvard§	Yes			No	Yes			No
Howard*	Yes		Yes		Yes		Yes	
Illinois*	Yes		Yes		Yes		Yes	
Indiana§		No		No		No		No
Iowa‡		No		No		No		No
Jefferson M. Coll.†	Yes		Yes			No		No
Johns Hopkins‡	Yes			No		No		No
Kansas‡	Yes			No		No	Yes	
Long Island Coll. Med.†	Yes		Yes		Yes			No
Louisville*	Yes		Yes		Yes		Yes	
Louisiana§	Yes		Yes		Yes		Yes	
Loyola*	Yes		Yes		Yes		Yes	
Marquette*	Yes		Yes		Yes		Yes	
Maryland†	Yes		Yes		Yes			No
Meharry M. Coll.§		No		No		No		No
Michigan‡	Yes		Yes			No		No
Minnesota*	Yes		Yes		Yes		Yes	
Nebraska†	Yes		Yes		Yes			No
New York M. Coll.*	Yes		Yes		Yes		Yes	
New York U.‡	Yes			No		No		No
Northwestern*	Yes		Yes		Yes		Yes	
Ohio*	Yes		Yes		Yes		Yes	
Oklahoma†	Yes		Yes		Yes			No
Oregon†	Yes			No	Yes		Yes	
Pennsylvania*	Yes		Yes		Yes		Yes	
Pittsburgh*	Yes		Yes		Yes		Yes	
Rochester*	Yes		Yes		Yes		Yes	
St. Louis*	Yes		Yes		Yes		Yes	
M. Coll. State of So. Carolina§		No		No		No		No
Stanford§	Yes			No		No		No
Syracuse*	Yes		Yes		Yes		Yes	
Temple*	Yes		Yes		Yes		Yes	
Tennessee§	No Reply							
Texas‡	Yes		Yes			No		No
Tufts M. Coll.†	Yes		Yes		Yes			No
Tulane‡	Yes		Yes			No		No
Vanderbilt*	Yes		Yes		Yes		Yes	
Vermont*	Yes		Yes		Yes		Yes	
Virginia*	Yes		Yes		Yes		Yes	
M. Coll. of Virginia*	Yes		Yes		Yes		Yes	
Washington*	Yes		Yes		Yes		Yes	
Wayne§	Yes			No		No		No
Western Reserve*	Yes		Yes		Yes		Yes	
Wisconsin*	Yes		Yes		Yes		Yes	
Woman's M. Coll.‡	Yes		Yes			No		No
Yale‡	Yes		Yes			No		No
	57	9	47	19	44	22	36	30

*Fulfills recommendations for minimum allergy curriculum.
†Minor deficiencies in allergy curriculum.
‡Inadequate instruction in allergy.
§Little or no organized instruction in allergy.

Certified in Allergy

The American Board of Internal Medicine has announced that the following candidates were certified in Allergy at the oral examination held in Chicago, April 24 to 26, 1947.

L. J. Courtright, San Francisco, Calif.
Iredell M. Hinnant, Cleveland, Ohio
Julian Rowe Kaufman, Louisville, Ky.
Frank Perlman, Portland, Oregon.
Charles B. Shuey, Dallas, Texas
Sidney Friedlaender, Detroit, Mich.

At the oral examinations held in Philadelphia, June 5-7, 1947, the following candidates were certified in Allergy.

Homer A. Howes, Detroit, Mich.
Emanuel Schwartz, Brooklyn, N. Y.
Howard C. Leopold, Philadelphia, Pa.
David E. Silberman, Bronx, N. Y.

A program concerning Antihistamine Agents in Allergy under the auspices of the New York Academy of Sciences will be given on October 3 to 4, 1947, at Central Park, West and 79th street. Those desiring to allow the Conference may do so by making a request in writing to the Executive Secretary of the Academy.

Program

Friday Morning, October 3, 9:30 to 12:30

Chairman: Dr. Frederick F. Yonkman

1. Sir Henry H. Dale, formerly Director of the National Institute for Medical Research, Mount Vernon House, N.W. 3, England
   The Pharmacodynamics of Histamine
2. Dr. Carl A. Dragstedt, Professor of Pharmacology, Northwestern University Medical School, Chicago, Illinois
   The Role of Histamine and Other Metabolites in Anaphylaxis
3. Dr. M. Rocha e Silva, Professor of Pharmacology and Biochemistry, Instituto Biologica, Sao Paulo, Brazil
   The Role of Blood Platelets and Leucocytes in Anaphylaxis

Friday Afternoon, October 3, 2:00 to 5:00

Chairman: Dr. Robert Cooke

4. Dr. M. W. Chase, Rockefeller Institute, New York City
   The Immunologic Aspects of Anaphylaxis and Allergy
5. Dr. E. T. Waters, Banting and Best Department of Medical Research and Department of Physiology, University of Toronto, Toronto, Canada
   The Detoxification of Histamine
6. Dr. N. Fell, Camp Detrick, Frederick, Maryland
   Histamine-Azo-Proteins in Anaphylaxis and Allergy

Saturday Morning, October 4, 9:30 to 12:30

Chairman: Dr. George Rieveschel, Jr.

7. Dr. D. Bovet, Professor of Pharmacology, University of Rome, Italy
   Introduction to Antihistamine Agents and Antergan Derivatives
8. Dr. Rudolf L. Mayer, Division of Research, Ciba Pharmaceutical Products, Inc., Summit, New Jersey
   The Activity of Pyribenzamine and Related Compounds With Special Reference to Their Mode of Action
9. Dr. Earl R. Loew, Department of Pharmacology, University of Illinois College of Medicine, Chicago, Illinois
   The Pharmacology of Benadryl and the Specificity of Antihistamine Drugs

Saturday Afternoon, October 4, 2:00 to 5:00

Chairman: Dr. Sanford B. Hooker

10. Dr. Rolf Meier, Medical Director, Ciba Limited, Basle, Switzerland and Professor of Pharmacology and Therapeutics, University of Basle, Switzerland
    Antistine and Related Imidazolines
11. Dr. Charles F. Code, The Mayo Foundation, Rochester, Minnesota
    The Mechanism of Action of Antihistamine Agents With Special Reference to Their Mode of Action in the Skin
12. Dr. Samuel M. Feinberg, Department of Allergy, Northwestern University Medical School, Chicago, Illinois
    Antihistamine Therapy, Experimental and Clinical Correlation

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The University of Oregon Medical School, located in Portland, during the past year has made allergy a division of Internal medicine with Dr. Robert L. Benson as Chairman of that division. Dr. Roy Matteri, Dr. Merle Moore and Dr. Frank Perlman assist him in the teaching of junior and senior medical students. The extent of this has included six lectures to the juniors and eleven to the seniors. In addition, the senior students receive one weekly session of two hours in allergy clinics for one term. In the Hospital a teaching program has been arranged for the residents in medicine in which they make rounds with one of the allergists on the staff to see allergy consultations and follow-up in the Out-patient department, allergic cases that have been discharged from the Hospital. Each medical resident is required to spend four months on this service.

The Allergy Unit of the University of Illinois Professional Colleges of Medicine and Pharmacy offers a twelve-month course in Allergy, October, 1947, to October, 1948.

The Michigan Allergy Society is participating in the scientific exhibit of the Michigan State Medical Society to be held in September. Doctors Credille, Insley and Fenton will be in charge of the exhibit which will include information regarding skin testing, anti-dust programs and the prevalence of common allergens.

Newly elected officers of the Chicago Society of Allergy for 1947-1948 are President, Theodore Bernstein; President Elect, E. G. Tatge; Secretary-Treasurer, Morris Kaplan.

At the Post-Graduate Clinics held in June by the Emory University Medical Alumni Association in Atlanta, an afternoon panel program on Allergy was held. The Moderator was Dr. Mason I. Lowance and the discussors were Dr. Clarence Laws, Dr. William Crowe, Dr. Edgar Denstan and Dr. Charles Stone.

In Dallas, Texas, there is a museum of health which contains a pollen exhibit.

Doctor William T. Penfound has been appointed Professor of Plant Sciences at the University of Oklahoma. Doctor Penfound has contributed several articles of interest to Allergists.

Dr. Narcisse F. Thiberge has been appointed Emeritus Clinical Professor of Medicine at Louisiana State University. On July 1, he will resign from active teaching where he has been associated with the Department of Medicine since the founding of the Medical School. In his early years, Dr. Thiberge was associated with the late Dr. W. Scheppergrell and it is said that he has administered an allergy clinic longer than anyone else in the United States.

Doctor David P. Barr, Professor of Medicine at Cornell and Physician in Chief to the New York Hospital, in his recent five-year report, has the following to say about allergy as a sub-specialty of medicine:

"It needs thorough revision not only here (New York Hospital) but in similar institutions. Without abandoning or depreciating the practical applications in hay fever and other forms of clinical hypersensitization, the emphasis should be shifted to a study of the principles of immunity as they apply to general medicine. Closer correlations with the department of immunology in the medical school, with the infectious disease ward and with similar activities in pediatrics and other clinical departments are important in activating a worthy enterprise in applied immunology."

Speaking of the work of the Allergy Clinic in the Outpatient Department he further states, "Hay fever, asthma, urticaria, and other conditions dependent upon sensitization are among the commonest of human ills. Indeed it has been estimated that approximately 10 per cent of the entire population suffers at one time or another from some allergic symptoms. Incapacitating and frequently recurring, allergic diseases require expert diagnosis and prolonged treatment by special methods which cannot be undertaken in a general clinic. The Allergy Clinic has long been one of the largest in the Outpatient Department. . . . During 1946 it has been possible to assign to the Allergy Clinic members of the House Staff on a rotating basis, thereby aiding the development of the enterprise and greatly enriching the experience and the scope of clinical training of the participants. The Allergy Clinic is one of the activities of the Department of Medicine which deserves further development and closer integration not only with other clinics and the wards, but also with the Department of Immunology in the Medical College."

The new Directory of the American Academy of Allergy has recently been distributed and supersedes the one compiled by Dr. Spain and published in the JOURNAL in 1945-1946. Only one who has worked with lists such as these can appreciate the seemingly endless time spent in assembling relevant information, and the meticulous attention to detail that is required.

The Directory is surprisingly complete when one considers the enlarged membership of the Academy, and it is a most useful reference. Acknowledgment with appreciation is made to Dr. Karl Figley who compiled it, on behalf of the Academy.